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SYNTHESIS OF ANTIDOTES FOR ORGANOPHOSPHORUS ACETYLCHOLINESTERASE INHIBITORS

ANNUAL/FINAL REPORT

RICHARD J. SUNDBERG

AUGUST 30, 1991

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13. ABSTRACT *(Maximum 200 words)*

This report describes the preparation of 73 new compounds prepared for evaluation as antidotes and/or prophylactic agents against the toxicity of organophosphorus acetylcholinesterase inhibitors. The compounds prepared included: heteroaromatic bis-cations (11 examples); heteroaromatic mono-cations (13 examples); phenoxymethyl heteroaromatic carbamates (12 examples); imidazopyridinium salts (32 examples); and miscellaneous compounds (5 examples). The preparative methods are described. For many compound in vitro activity as inhibitors of acetylcholinesterase is given. Some compounds have also been evaluated for in vivo prophylactic and antidotal activity.

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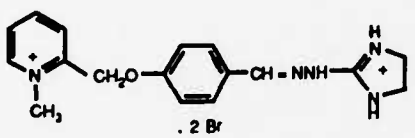
I. Introduction

The objective of this project was to prepare new compounds for evaluation of both antidotal and prophylactic activity against the lethal toxicity of organophosphorus acetylcholinesterase (AChE) inhibitors. There are two classical approaches to such activity (1) reversible protection of the essential serine residue in AChE against phosphorylation; (2) reactivation of the AChE by nucleophilic displacement of the phosphoryl group. <1> This project resulted in synthesis of 75 new compounds. The report describes the structure, means of synthesis and observed biological activity of these compounds. Possible structure-activity relationships are discussed.

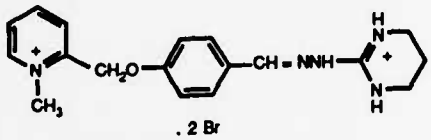
The project was initiated on the basis of antidotal activity observed for two compounds which were previously prepared in connection with a study of anti-parasitic compounds. These compounds were bis-cations featuring a pyridylmethyl ether moiety.



. 2 Br

BL08205

70-90% survival at 2 LD_{50} GD

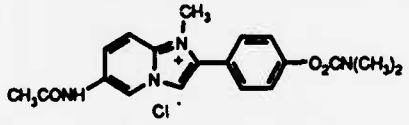


. 2 Br

BL08042

70% survival at 2 LD_{50} GD

Another compound, related to the extensive series of imidazo[1,2-a]pyridines prepared in the anti-parasitic work was promising in the pretreatment screen.



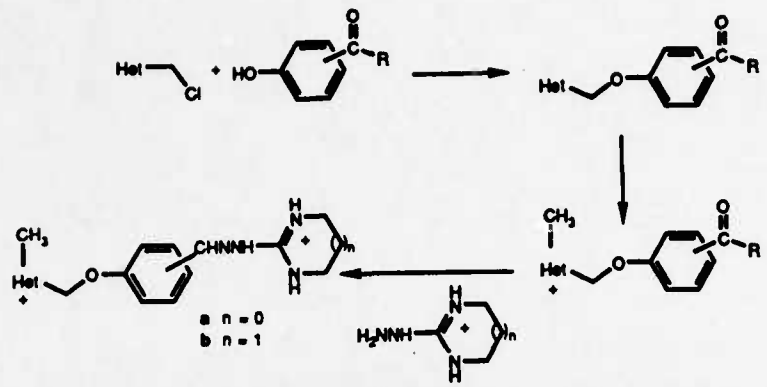
BL55142

100% survival at 15 min pretreatment prior to 2 LD_{50} GD

These compounds served as the leads in attempts to (1) recognize the crucial structural requirements for activity and (2) optimize the antidotal and/or prophylactic effects. It is convenient to consider the compounds in three groups: (1) bis-cations, (2) non-carbamate heteroaromatics and (3) heteroaromatic carbamates. The synthetic methods and biological activity will be discussed subsequently for these three categories. The compounds which were prepared are given in a chronological and numerical (WRAIR bottle number) order in Table 1.

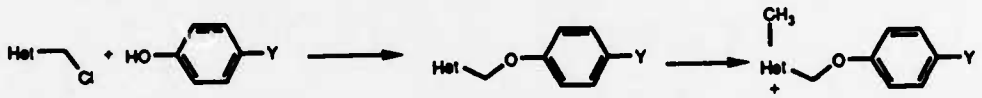
II. Synthetic Methods

The methods for the bis-cationic compounds follow those developed during the course of our investigation of related compounds with regard to antiparasitic activity. <2>. The heteroromatic ring was usually incorporated by alkylation of a hydroxybenzaldehyde. The resulting aldehyde was then quaternized with methyl tosylate or methyl iodide. The aldehyde was then converted to a guanylhydrazone using a cyclic guanylhydrazine.

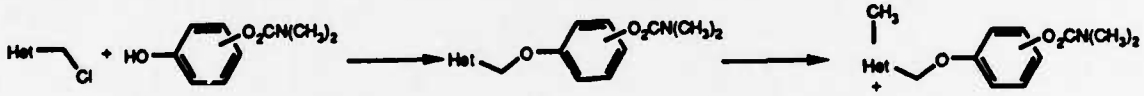


In this work cyclic guanylhydrazones of both meta and para formyl (R=H) and para acetyl ($R=CH_3$) derivatives were synthesized. The heterocyclic ring was either pyridine, imidazole or imidazo[1,2-a]pyridine. The point of substitution was limited to the 2-position of the ring.

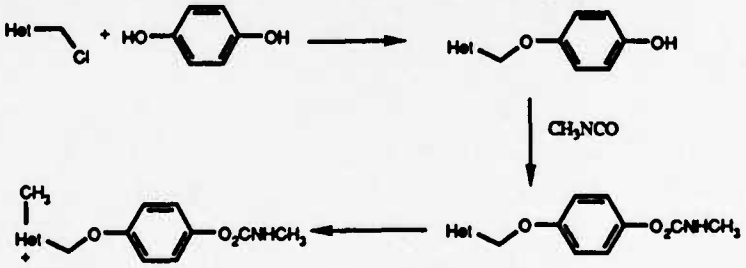
A series of pyridinium and imidazolium salts was prepared to determine the functionality required for activity. The appropriate chloromethyl heterocycle was used to alkylate a substituted phenol.



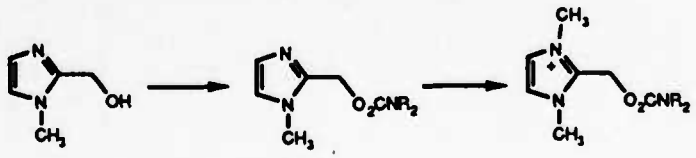
A major group of compounds which was prepared comprised aryloxylmethyl N,N-dimethylcarbamates derived from pyridine, imidazole, imidazo[1,2-a]-pyridine, benzimidazole and isoquinoline. These compounds were usually prepared by alkylation of a monocarbamoylated dihydroxybenzene.



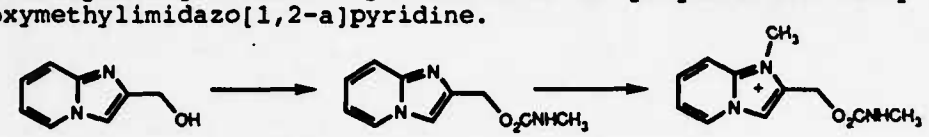
A smaller number of the less stable monomethylcarbamates were prepared. These were prepared by carbamoylation of the corresponding phenols.



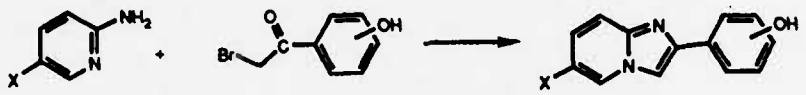
A few compounds were prepared by specific procedures. The N,N-dimethyl and N-methyl carbamates of 1,3-dimethyl-2-hydroxymethylimidazolium were prepared from 2-hydroxymethyl-1-methylimidazole.



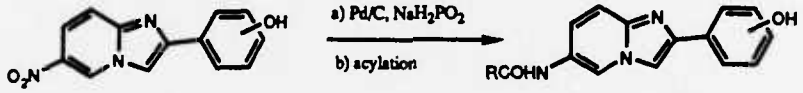
The corresponding N-monomethyl carbamate was prepared similarly from 2-hydroxymethylimidazo[1,2-a]pyridine.



An extensive series of 2-arylimidazo[1,2-a]pyridinium salts having a carbamate functionality on the aryl ring was prepared. These compounds were obtained from a substituted 2-aminopyridine and meta- or para-hydroxy phenacyl bromide. The standard imidazo[1,2-a]pyridine synthesis gave a 2-(hydroxyphenyl)imidazo[1,2-a]pyridine.



Where necessary, the substituent X was then used to introduce modified functionality. For example, starting with 2-amino-5-nitropyridine a 6-nitroimidazopyridine was obtained. The nitro group served as the precursor of various amido substituents.



Carbamoylation and quaternization were then carried out. N,N-Dimethylcarbamates were made from the phenol with N,N-dimethylcarbamoyl chloride and monomethyl carbamates were made using methyl isocyanate. Quaternization was done with methyl iodide or methyl tosylate. The N,N-dimethylcarbamates were usually converted to chlorides by ion exchange. The monomethyl carbamates were unstable to ion exchange and were usually submitted as iodides.

All compounds submitted for biological evaluation were characterized by IR and NMR spectra and by elemental analysis. In all cases, the observed spectra were consistent with the assigned structure. The compounds were also subjected to elemental analysis and many were found to be hydrates.

III. Biological Data

The biological data which has been collected for the newly synthesized compounds is given in Table 2. Compounds are classified in three groups: bis-Cations; non-Carbamate Heteroaromatic Salts and Heteroaromatic Carbamates, with the latter group being further subdivided by ring system. Data for the standard protocols for pretreatment or antidotal screens are given. When no data is given, the results of the corresponding screen has not been reported to us.

Many of the compounds were examined in vitro as inhibitors of electric eel AChE following the procedure of Ellman.<4> This data is reported as the concentration effecting 50% inhibition, as determined from a sigmoid plot of 4-6 concentrations. Some of the compounds were also tested for ability to inhibit fetal bovine serum (FBS) AChE.<5> These data gave either as IC_{10} and IC_{90} values or as % inhibition at 80μM.

Some compounds were also tested for reactivation of GA and VX inhibited FBS AChE.<5> The compounds are designated PASS if the statistical criteria for activity were reached 80μM. Similar data are given for reduction of the rate of aging of FBS AChE inhibited by GD.

A. Bis-Cations

The lead compounds BL08205 and BL09042 had provided confirmed activity in the antidotal screen against 2 LD_{50} of GD. While these bis-cations share some structural similarity with oxime-type reactivators (pyridinium ring, oxymethylene group), the lack of a nucleophilic site would appear to exclude AChE reactivation as the mechanism of action. A number of other bis-cations were prepared in order to develop structure-activity relationships. The 1,3-dimethylimidazolium salts corresponding to BL08205 and BL09042 were prepared (BM01292, BM01274). The pyridinium salts with meta substitution (BM01701, BM02057) and the corresponding 1,3-dimethylimidazolium salts (BM02039, BM02600) were prepared. The acetyl analogs (BM02002, BM02021) were prepared. Finally, the imidazo[1,2-a]pyridiniun salts were tested (BM02048, BM02619).

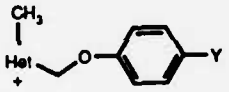
None of these compounds approached the activity of the lead compounds, and none showed potential as antidotes according to the established criteria. Most of the compounds were also tested in the pretreatment screen, but none showed promising activity.

Several of the compounds were examined as AChE inhibitors. The bis-cationics BL08205, BL09042, BM01274, BM01292, BM01701, BM02002, BM02011, BM02039 and BM02048 showed IC_{50} values in the low micromolar range.

B. Non-Carbamate Heteroaromatic Monocations

A series of pyridinium and imidazolium salts which lacked the second cationic center was also prepared. Most of these were 4'-substituted derivatives as summarized in Scheme 1.

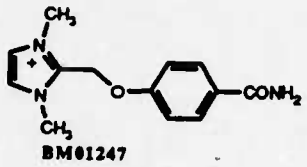
Scheme 1



HETEROCYCLE	4'-SUBSTITUENT	BOTTLE NUMBER
2-pyridinium	$CH{=}NNHCSNH_2$	BL58625
2-pyridinium	CH=NN	BL58634
2-pyridinium	OCH_3	BM00188
2-pyridinium	H	BM00197
2-pyridinium	$C(CH_3)_3$	BM00204
2-pyridinium	CH=NNHCO	BM00213
2-pyridinium	CH=O	BM00571
2-pyridinium	$CONH_2$	BM00580
2-pyridinium	CH=NOH	BM00599
2-imidazolium	$CH{=}NNHCSNH_2$	BM00606
2-imidazolium	CH=NOH	BM01238
2-imidazolium	$CONH_2$	BM01247

Of these compounds the only significant activity noted was for the imidazolium amide BM01247 which showed both protective and antidotal effects

at 49 mg/kg.

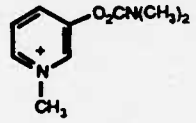


Activity at 49 mg/Kg
maximum survival
Pretreatment 90%, 100%
Antidote 70%

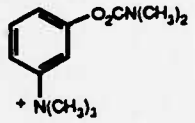
These results indicate that the monocationic pyridinium compounds lacking a second cationic group have little effect on AChE activity. Structure BM01247 is quite similar to some of the heteroaromatic carbamates, and will be reconsidered in Section IV.

C. Heteromatic Carbamates

In a general sense, these compounds can be related to pyridostigmine and to neostigmine which combine a cationic center to effect binding at the AChE anionic site and a carbamate group which presumably effects reversible carbamoylation. Another structural criterion which pertains to these compounds is the distance separating the cationic and carbamate centers which may ideally be 4.9 Å, the separation in acetylcholine.

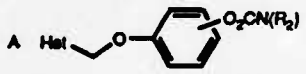


Pyridostigmine

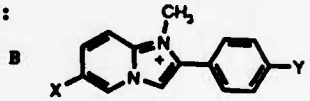


Neostigmine

Our compounds can be subdivided into two classes: (a) A variety of 2-(phenoxymethyl)heteromatics of general structure A;



(b) Imidazo[1,2-a] pyridines based on lead compound BL55142:

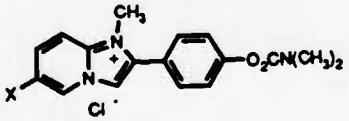


We will first discuss these groups separately and then draw comparisons between them.

C.1 Imidazo[1,2-a]pyridinium Salts

The majority of the imidazo[1,2-a]pyridinium salts are structural analogs of BL55142 in which the 6-acetamido substituent has been replaced by a variety of other substituents as shown in Table 3.

Table 3.



COMPOUND	X	MAX SURVIVAL PRE	ANTI	COMPOUND	X	MAX SURVIVAL PRE	ANTI
BL55142	CH_3CONH-	100	30	BM04935	$CH_3NHCONH$-	80	80
BM02020	H-	100	30	BM05567	$CH_3CON(CH_3)$-	100	70
BM04337	$(CH_3)_2NCO_2$-	60	60	BM05978	CH_3-		
BM04346	CH_3O_2CNH-	50	60	BM06484	CF_3-		
BM04364	HCONH-	90	90	BM07641	Cl-		
BM04926	PhCONH-	50	30	BM07696	CH_3O-		

Thus these compounds show a quite consistent pattern of activity in the

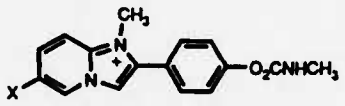
pretreatment screen. None is conspicuously superior to BL55142, but the activity of M02020, BM04364 and BM05567 are comparable.

Table 4.

BM02020 DOSE	SURVIVAL 15	60	BM04364 DOSE	SURVIVAL 15	60	BM05567 DOSE	SURVIVAL 15	60
5	80	90	0.8	90	90	6.2	60	70
20	80	100	2.1	70	70	25	60	100
80	10	60	12.4	20	80	100	50	80

Several of the N-monomethyl carbamates were also prepared.

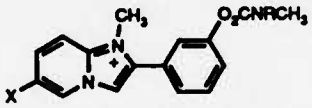
Table 5.



Compound	X	Maximum Survival Pre	Anti
BM02637	H-		
BM03198	CH_3CONH-	80	70
BM05969	CH_3-		
BM06493	CF_3-		
BM06706	Cl-		

Another series of compounds placed the carbamate substituent as the 3'-position of the phenyl substitient.

Table 6.

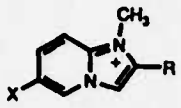


R=CH_3	X	Maximum Survival Pre	Anti	R=H	X	Maximum Survival Pre	Anti
BM03689	CH_3CONH-	60	40	BM03670	CH_3CONH-	XX	XX
BM06475	H-			BM05987	H-		
BM06680	CH_3-			BM06699	CH_3		
BM07669	Cl-			BM07678	Cl-		
BM07687	CF_3-			BM07703	CF_3-		
BM08620	7-CH_3						
BM08639	OCH_3-						

C.2 Related Imidazo[1,2-1]pyridinium Salts

Several other imidazo[1,2-a]pyridines were prepared to establish structure-activity limits. These included compounds where the carbamate substituent was placed on the imidazo[1,2-a]pyridine ring or removed entirely.

Table 7.

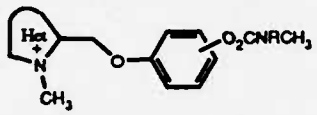


	X	R	Maximum Survival Pre	Anti
BM03189	CH_3CONH	C_6H_5	10	10
BM06500	CH_3CONH-	H		
BM07650	CH_3O_2CNH-	C_6H_5		
BM08648	$(CH_3)_2NCO_2-$	C_6H_5		

C.3 Carbamates Derived from Phenoxymethyl Heteroaromatic Cations

The general structure of these compounds is shown below and encompasses ortho, meta and para carbamates. The maximum survival rate observed under both pretreatment and antidote conditions is given in Table 8.

Table 8.



	Het[a]	Pos	R	Maximum Survival Pre	Anti
BM01256	pyr	4'	H	100	60
BM01265	pyr	4'	CH_3	100	40
BM01729	pyr	3'	CH_3		
BM09332	pyr	2'	CH_3		
BM01710	imid	4'	CH_3		60
BM01738	imid	3'	CH_3	60	30
BM09341	imid	2'	CH_3		
BM02628	impyr	4'	CH_3	70	
BM08657	impyr	3'	CH_3		
BM09298	benzim	3'	CH_3		
BM09305	benzim	4'	CH_3		
BM09314	quin	3'	CH_3		
BM09323	quin	4'	CH_3		

a: pyr = 1-methylPyridinium, imid = 1,3-dimethylimidazolium, impyr = 1-methylimidazo[1,2-a]pyridinium; benzim = 1,3-dimethylbenzimidazolium; quin = 1-methylquinolinium.

IV. Discussion

The interpretation of the biological results must remain somewhat tentative since in vivo data have not yet been obtained for many of the ompounds. We do have in vitro AChE (electric eel) inhibition data for representataives of each of the subclasses and these, along with the more scattered in vivo results will serve as the basis for discussion and tentative conclusions.

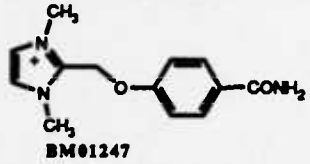
A. Bis-Cations

Eleven bis-cationic compounds related to the original lead compounds BL08205 and BL09042 were synthesized and submitted for evaluation. None of the new compounds showed promise in the antidotal or prophylactic screens. The structural variations done included: replacement of imidazolium and imidazo[1,2-a]pyridinium for pyridinium; meta-substitution of the guanylhydrazone function; and use of an acetyl for formyl connection to the guanylhydrazone. In view of the negative results, little new information about structure-activity relationships has been developed. Interestingly, the compounds are active as in vitro AChE inhibitors. The most likely explanation is that

they act as reversibly bound competitive inhibitors on the basis of their cationic nature. Other types of bis-cationic compounds are known to have inhibiting activity on AChE.<6>

B. Non-Carbamate Heteroaromatic Mono Cations

Nine pyridinium and three imidazolium compounds were examined. Most exhibited only modest AChE inhibition (>50μM) and only marginal in vivo activity. The possible exception is BM01247, an imidazolium carboxamide, which showed both antidotal and prophylactic activity.



BM01247

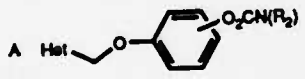
Antidote 70% survival at 49 mg/Kg
Prophylactic 90 - 100% survival at 49 mg/Kg

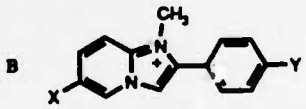
The compound showed little in vitro AChE inhibition (IC_{50}>100μM) so evidently does not act directly on AChE. Further studies of this compound such as the preparation of the meta analog and both the meta and para N,N-dimethyl analogs would be of interest.

While the non-carbamate pyridinium group of compounds does not include likely prophylactic or antidotal canditates, this group of pyridinium and imidazolium mono-cations provide a useful reference point for the carbamate series.

C. Heteroaromatic Carbamates

Fourty-eight compounds fall into this category and the discussion will be subdivided into the phenoxymethyl compounds represented by general structure **A** and the imidazo[1,2a] pyridinium compounds represented by general structure **B**. A few miscellaneous compounds will be considered at the end of this section.



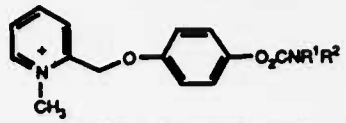


Het=
- 1-Methyl-2-pyridinium
- 1,3-Dimethyl-2-imidazolium
- 1-Methyl-2-quinolinium
- 1,3-Dimethylbenzimidazolium
- 1-Methylimidazo[1,2-a]pyridinium

X = substituent or O_2CNR_2
y = O_2CNR_2 or substituent

The phenoxymethyl compounds include all the meta and para substituted N,N-dimethyl carbamates, the ortho N,N-dimethylcarbamate for the first two heterocycles listed above and the para monomethyl-carbamate in the pyriclinium series. The AChE (eel) IC_{50} data is compiled in Table 2. All are quite potent with B01738 and BM09332 being active in the nanomolar range. Only limited in vivo data is available but the para-substituted pyridinium carbamates both exhibit excellent activity in the pretreatment screen.

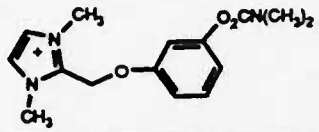
Table 9.



Compound	Dose	Maximum Survival 15 Min	60 Min	R^1	R^2
BM01265	6.25	100	90	CH_3	CH_3
BM01265	15.6	90	90	CH_3	CH_3
BM01256	0.9	80	100	H	CH_3
BM01256	3.5	60	100	H	CH_3

The very potent AChE inhibitor BM01738, which has a very low LD_{50} (~0.4 mg/kg) does not achieve this level of effectiveness. This probably due to the low dose required by its high toxicity.

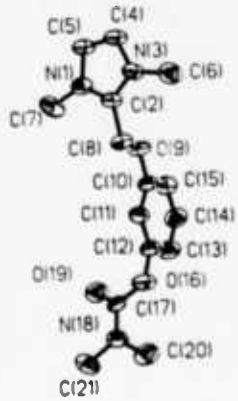
Table 10



Compound	Dose	Maximum Survival 15 Min	60 Min
BM01738	0.007	60	40
BM01738	0.03	40	40

Assuming that these compound function in the classic manner by carbamoylation of the active site serine, the salient feature of the data is that a rather wide variation in the placement of the cationic center and the carbamoyloxy function can be tolerated. Many earlier studies in the area have assumed that the 4.9Å separation should represent an ideal.<6> The considerably greater separation suggests considerable flexibility in the active site.

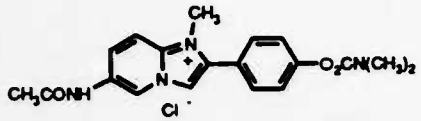
An X-ray crystal structure was done on the potent AChE inhibitor BM01738. The cationic (imidazole C-2) and carbonyl carbon are separated by 8.6 Å in the crystalline compound.



D. Imidazo[1,2-a]pyridinium Salts

The lead compound for this group was BL55142, which achieved 80-100% survival in the pretreatment screen.

Table 11.

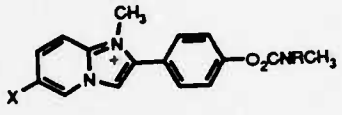


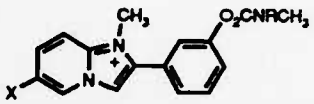
BL55142

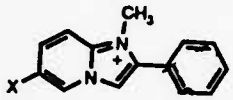
Compound	Dose	Maximum Survival 15 Min	60 Min
BL55142	1.5	100	90
BL55142	5.8	100	60
BL55142	23	50	70

Structural variation was done by replacing the acetamido substituent with a variety of groups. A number of these compounds were made with the carbamate group in the meta position. Several compounds in which the carbamate group was placed on the imidazo[1,2-a]pyridine ring were also made. Finally, a few truncated compounds were made to define the minimal requirements for activity.

Scheme 2.







Compound	X	R	Compound	X	R	Compound	X
BM02020	H	CH_3	BM03670	CH_3CONH-	H	BM03189	CH_3CONH-
BM02637	H	H	BM03689	CH_3CONH-	CH_3	BM07650	CH_3O_2CNH-
BM03198	CH_3CONH-	H	BM05987	H	H	BM08648	$(CH_3)_2NCO_2$-
BM04337	$(CH_3)_2NCO_2$-	CH_3	BM06475	H	CH_3		
BM04346	CH_3O_2CNH-	CH_3	BM06680	CH_3-	CH_3		
BM04364	HCONH-	CH_3	BM06699	CH_3-	H		
BM04917	CH_3SO_2NH-	CH_3	BM07669	Cl-	CH_3		
BM04926	PhCONH-	CH_3	BM07678	Cl-	H		
BM04935	$CH_3NHCONH$-	CH_3	BM07687	CF_3-	CH_3		
BM05567	CH_3CON-	CH_3	BM07703	CF_3-	H		
BM05969	CH_3-	H	BM08611	7-CH_3-	CH_3		
BM05978	CH_3-	CH_3	BM08639	CH_3O-	CH_3		
BM06484	CF_3-	CH_3					
BM06493	CF_3-	H					
BM06706	Cl-	H					
BM07641	Cl-	CH_3					
BM07696	CH_3O-	CH_3					
BM08620	7-CH_3	CH_3					

The IC_{50} values for inhibition of electric eel acetylcholinesterase are given in Table 2. Most were in the range 1-20 μM. In vivo data is available for some of the compounds and is also included in Table 2.

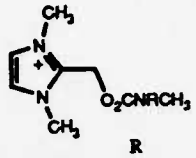
Structures which are closely related to the lead compound such as the formamide BM04364 and the N-methylacetamide BM05567 retained comparable prophylactic activity. The compound lacking the amido function altogether, BM02020, retains good in vivo activity. This data points to the carbamate group as the crucial functionality. This conclusion is supported by the lack of activity of the analogue BM03189 which lacks the carbamate functionality. The meta substituted analogue of the lead compound, BM03689 is somewhat less effective. No data are yet available on the less amide-like substituents such as methyl, methoxy, chloro and trifluoromethyl.

E. Miscellaneous Compounds.

A few compounds in which a carbamate group were attached to a hydroxymethyl heterocycle were made. These compounds approach the 4.9 Å separation of the cationic center and carbonyl group found in acetylcholine. While these

compounds were not active as AChE inhibitors, BM02646 showed excellent prophylactic activity.

Table 12.

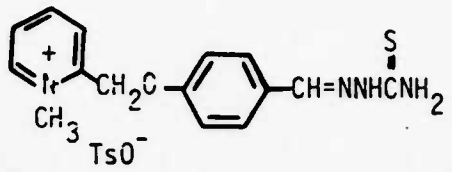
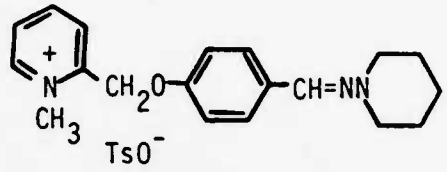
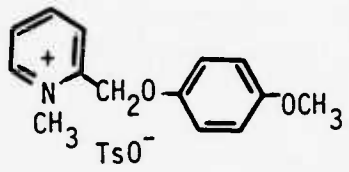
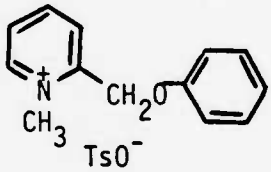
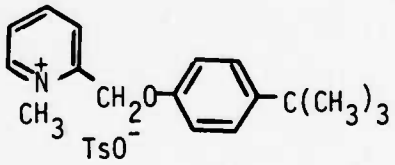
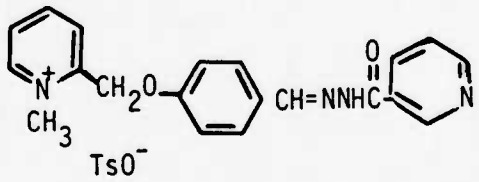
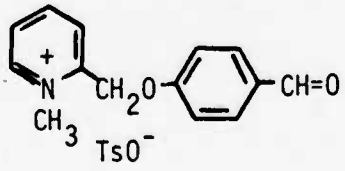


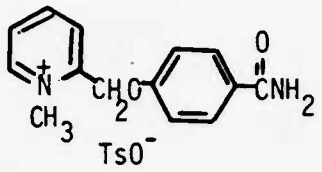
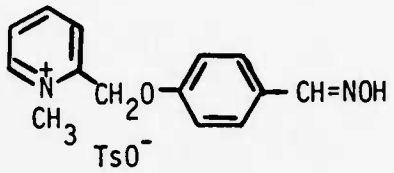
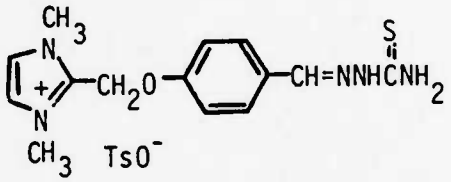
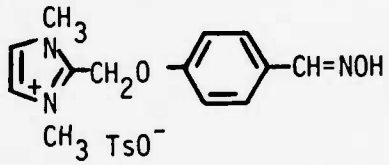
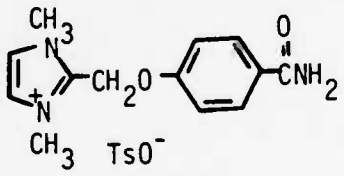
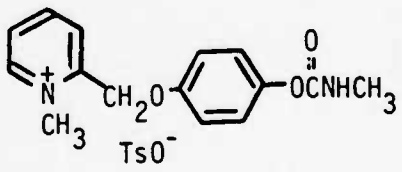
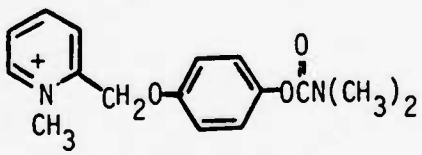
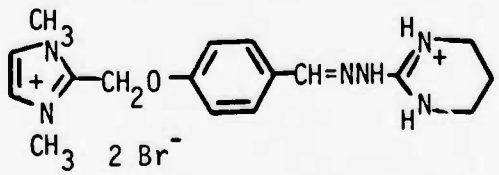
	R
BM02646	H
BM03698	CH_3

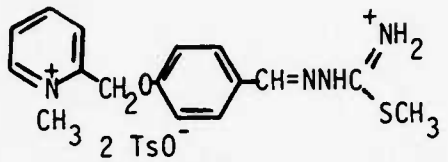
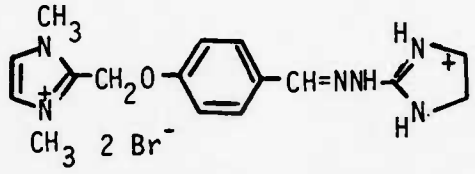
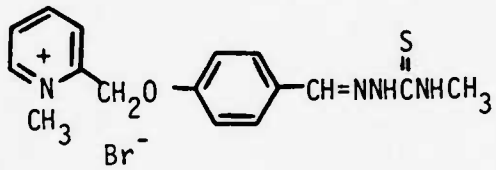
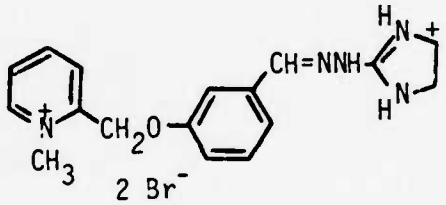
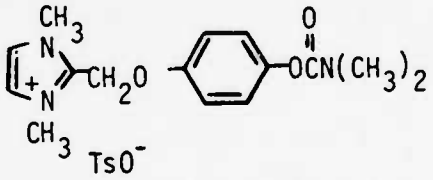
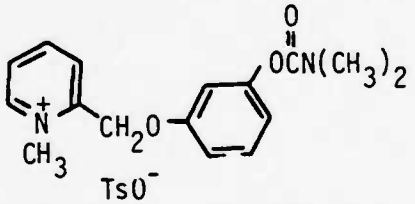
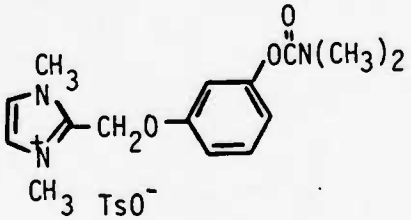
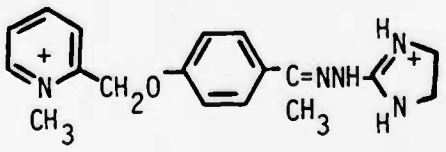
		Survival	
	Dose	15 Min	60 Min
BM02646	6.25	90	90
	25.0	90	100
	100	100	90

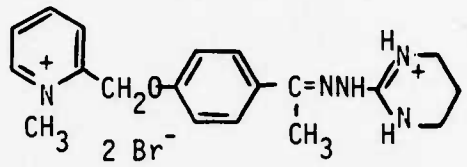
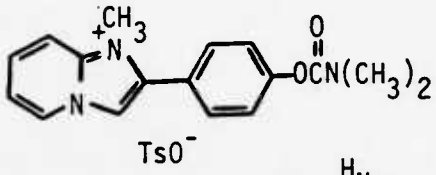
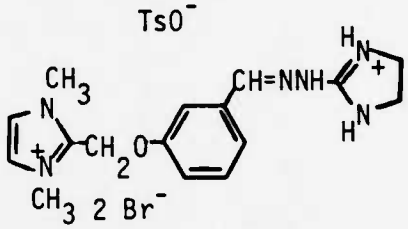
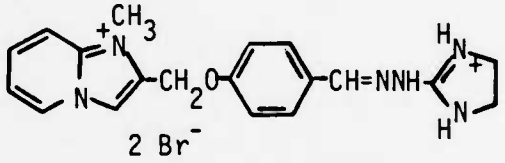
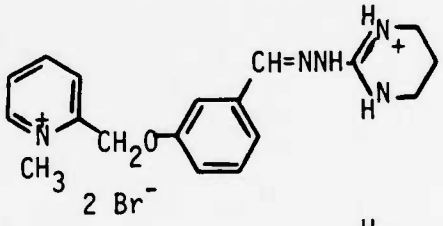
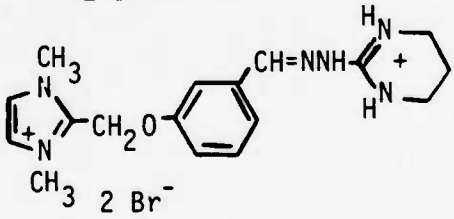
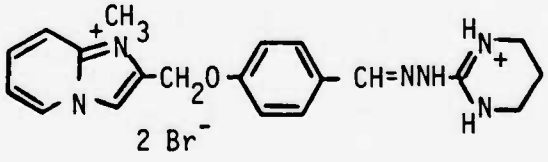
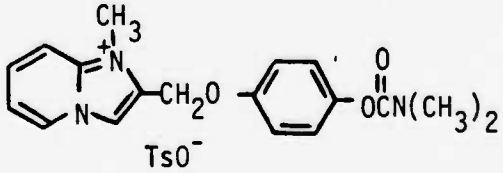
Clearly this lead is very interesting and should be followed up, for example, with the corresponding 2 pyridyl and 4-imidazyl derivatives. These compounds may be related to those described recently by Koolpe etal.<7> These compounds are imidazolium salts with one relatively complex nitrogen substituent and amido or methyl substituents at C-2.

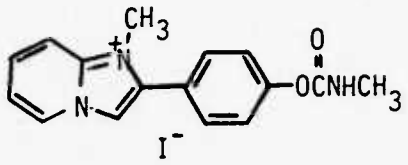
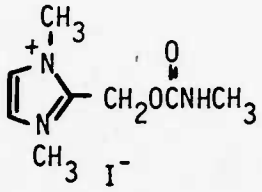
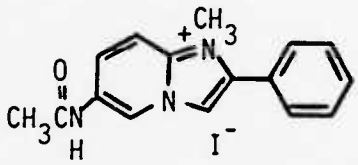
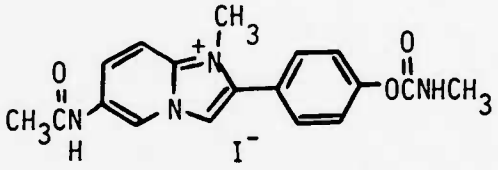
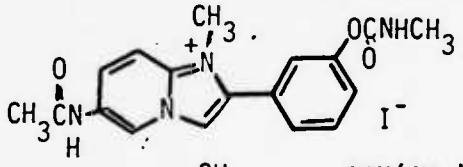
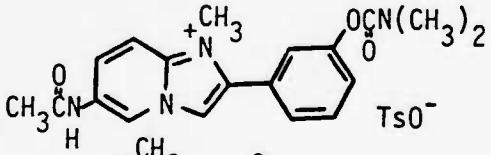
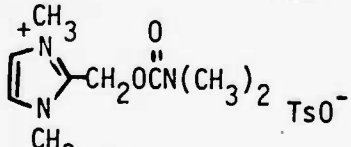
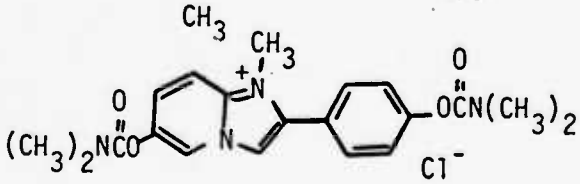
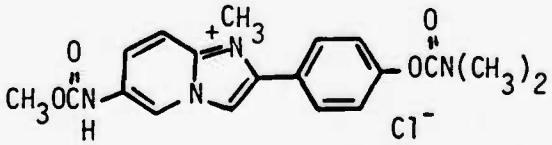
TABLE 1. Compounds Prepared and Submitted for Evaluation

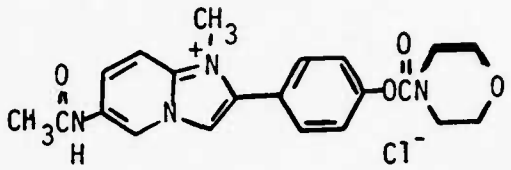
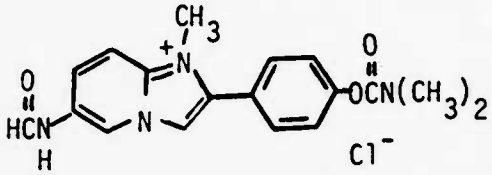
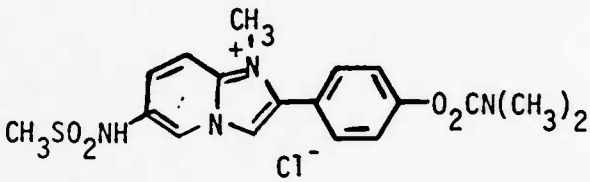
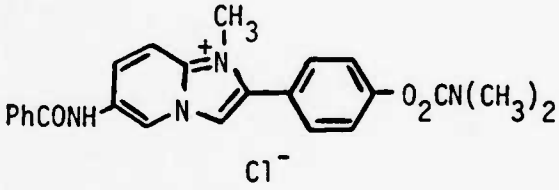
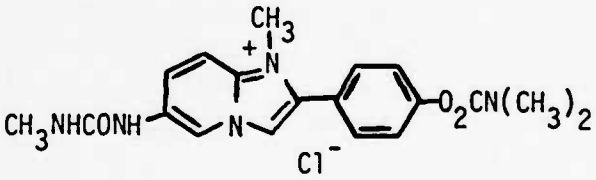
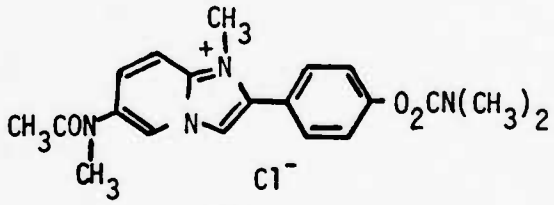
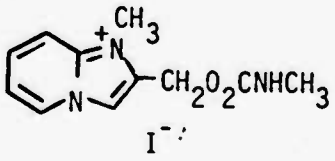
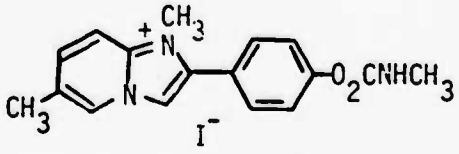
Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
JP-I-17	BL58625	10 May 89	
JP-I-20	BL58634	10 May 89	
DD-I-39-B	BM00188	12 Jul 89	
DD-I-40-B	BM00197	12 Jul 89	
DD-I-41-B	BM00204	12 Jul 89	
DD-I-42	BM00213	12 Jul 89	
DD-I-45-B	BM00571	4 Aug 89	

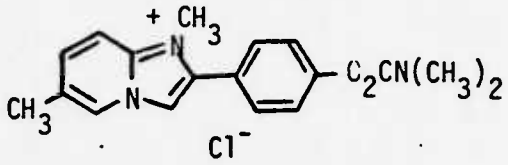
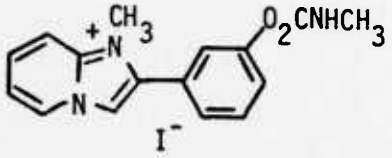
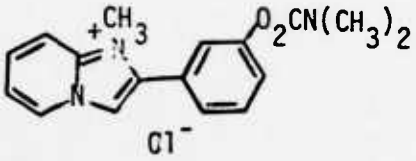
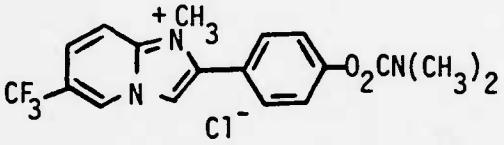
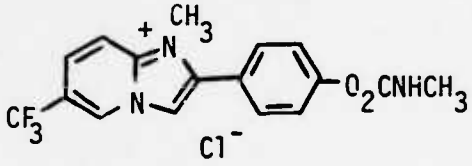
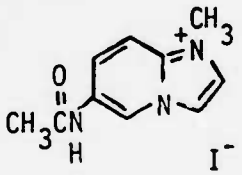
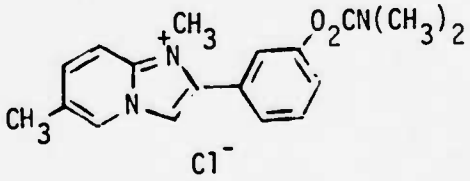
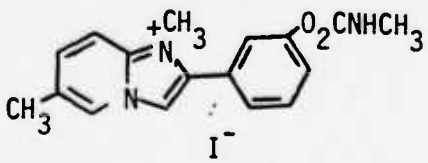
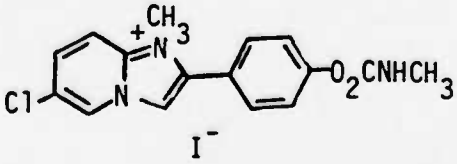
DD-I-48-B	BM00580	4 Aug 89	
DD-I-49-B	BM00599	4 Aug 89	
DD-I-53-B	BM00606	4 Aug 89	
DD-I-64	BM01238	12 Sep 89	
DD-I-69	BM01247	12 Sep 89	
DD-I-76-B	BM01256	12 Sep 89	
DD-I-77-B	BM01265	12 Sep 89	
JC-I-18-A	BM01274	12 Sep 89	

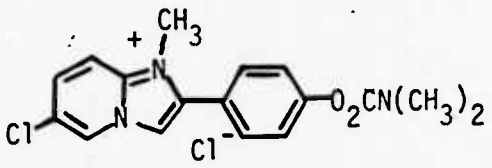
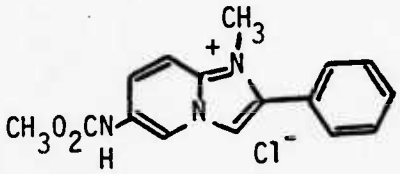
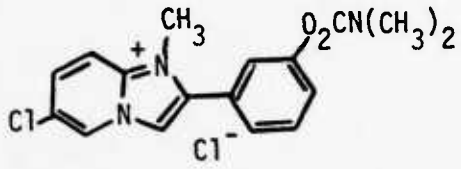
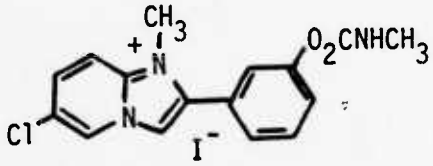
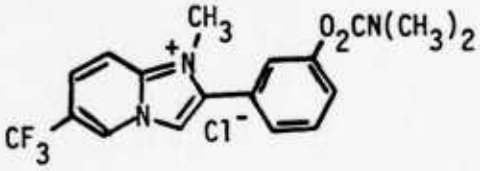
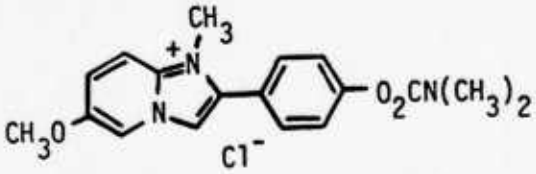
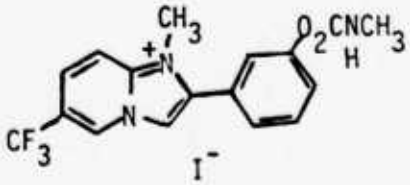
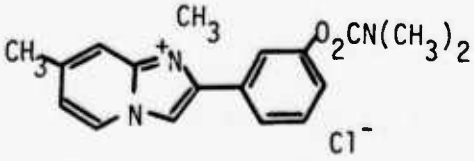
JC-I-19	BM01283	12 Sep 89	
JC-I-21-A	BM01292	12 Sep 89	
JC-I-44-B	BM01694	10 Oct 89	
JC-I-36-A	BM01701	10 Oct 89	
DD-I-82	BM01710	10 Oct 89	
DD-I-86	BM01729	10 Oct 89	
DD-I-87-B	BM01738	10 Oct 89	
DD-I-90	BM02002	6 Nov 89	

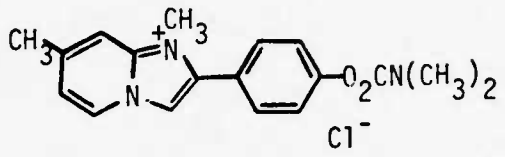
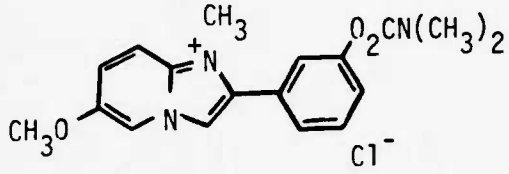
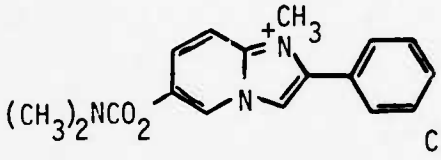
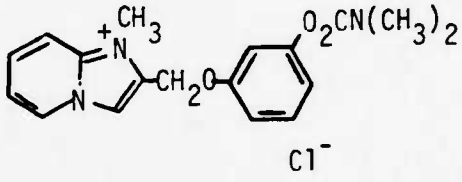
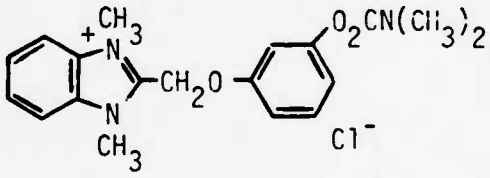
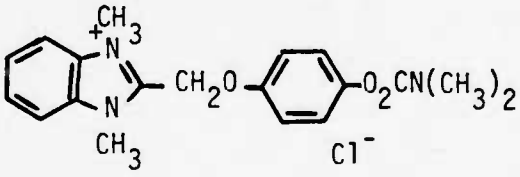
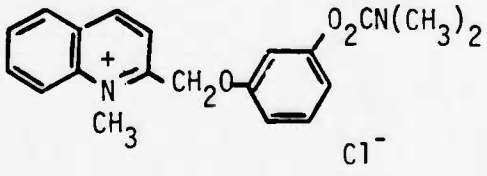
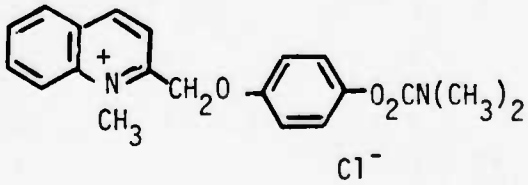
DD-I-90-A	BM02011	6 Nov 89	
DD-I-98	BM02020	6 Nov 89	
JC-I-44-A	BM02039	6 Nov 89	
JC-I-59	BM02048	6 Nov 89	
JC-I-63	BM02057	6 Nov 89	
JC-I-34-B	BM02600	6 Dec 89	
JC-I-58	BM02619	6 Dec 89	
JC-I-64-B	BM02628	6 Dec 89	

Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
JC-I-71	BM02637	6 Dec 89	
JC-I-72-A	BM02646	6 Dec 89	
DD-II-12	BM03189	4 Jan 90	
JC-I-77	BM03198	4 Jan 90	
DD-II-34	BM03670	13 Feb 90	
DD-II-45	BM03689	13 Feb 90	
DD-II-61	BM03698	13 Feb 90	
DD-II-75	BM04337	9 Apr 90	
DD-II-104	BM04346	9 Apr 90	

Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
DD-II-137	BM04355	9 Apr 90	
DD-II-140	BM04368	9 Apr 90	
DD-II-162	BM04917	29 May 90	
DD-II-163	BM04926	29 May 90	
DD-II-178	BM04935	29 May 90	
DD-III-1	BM05567	29 Jun 90	
DD-III-18	BM05950	13 Aug 90	
DD-III-24	BM05969	13 Aug 90	

Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
DD-III-28	BM05978	13 Aug 90	
DD-III-29	BM05987	13 Aug 90	
DD-III-34	BM06475	19 Sep 90	
DD-III-36	BM06484	19 Sep 90	
DD-III-37	BM06493	19 Sep 90	
DD-III-39	BM06500	19 Sep 90	
DD-III-49	BM06680	5 Oct 90	
DD-III-53	BM06699	5 Oct 90	
DD-III-55	BM06706	5 Oct 90	

Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
DD-III-61	BM07641	09 Jan 91	
DD-III-62	BM07650	09 Jan 91	
DD-III-100	BM07669	09 Jan 91	
DD-III-101	BM7678	09 Jan 91	
DD-III-112	BM07687	09 Jan 91	
DD-III-115	BM07696	09 Jan 91	
DD-III-117	BM07703	09 Jan 91	
DD-III-146	BM08611	4-10-91	

Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
DD-III-147	BM08620	4-10-91	
DD-III-158	BM08639	4-10-91	
DD-III-174	BM08648	4-10-91	
DD-III-178	BM08657	4-10-91	
DD-III-193	BM09298	7-1-91	
DD-III-194A	BM09305	7-1-91	
DD-IV-10	BM09314	7-1-91	
DD-IV-15	BM09323	7-1-91	

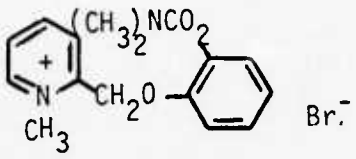
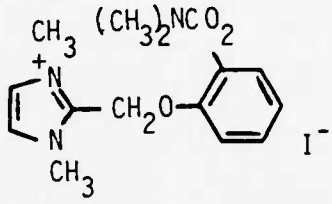
Our Sample Number	WRAIR Bottle Number	Date of Submission	Structure
DD-IV-16	BM09332	7-1-91	
DD-IV-20	BM09341	7-1-91	

Table II. Biological Results by Compound Category

A. Bis-Cations

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Inhibition F.B.S.[b]	Reactivation[c] GA	VX	GD	Dose	IN VIVO ASSAYS: Pretreatment 15 Min	Pretreatment 60 Min	Antidote
BM01274	JC-I-18-A	1.4	1.4	F	F	F	0.90			0
WR255941			105.5				3.8			10
BM01283	JC-I-19	19	34	P	F	P	1.1	30	40	0
WR268469							4.3	30	50	10
							17	30	30	20
BM01292	JC-I-21-A	1.5	3.3	F	F	F	0.3	0	10	0
WR255938			206.8				1.3	10	0	0
							5.0	0	0	20
BM01701	JC-I-36-A	4.6	58	P	P	P	0.15	50	10	0
WR268501							0.60	20	10	0
							2.40	20	20	0
BM02002	DD-I-90	2.2					0.07			0
WR268518							0.29			10
							1.15			0
BM02011	DD-I-90A	2.1	46	P	P	P	.62	10	0	10
WR268519							2.5	0	10	20
							10.0	0	20	10
BM02039	JC-I-44-A	4.6					4.0			20
WR268521										
BM02048	JC-I-59	2.7					3.1			10
WR268522							12.5			0
							50.0			10
BM02057	JC-I-63	2.5					0.12			10
WR268523							0.50			0
							2.0			10
BM02600	JC-I-34-B	1.7								
BM02619	JC-I-58	0.9								

B. Non-Carbamate Heteroaromatic Monocations

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Inhibition F.B.S.[b]	Reactivation[c] GA	Reactivation[c] VX	Reactivation[c] GD	Dose	IN VIVO ASSAYS: Pretreatment 15 Min	Pretreatment 60 Min	Antidote
BL58625	JP-I-17	20					12.5			20
WR268199							15.6	0	10	
							50			10
							62.5	0	0	
							250	20	30	
BL58634	JP-I-20	63					2.0	0	10	0
WR268231							8.0	30	0	0
							32.0	40	0	0
							62	0	0	
							250	0	20	
BM00188	DD-I-39-B	80					28.5			0
WR268360										
BM00197	DD-I-40-B	8.3		F	F	P		2.1		10
WR268361										
BM00204	DD-I-41-B	<100					4.9			10
WR268362										
BM00213	DD-I-42	2					0.5			0
WR268363							2.1			20
							8.5			20
BM00571	DD-I-45-B	141					6.2			0
WR268392							25			0
BM00580	DD-I-48-B	>100	7.1	F	F	F	47.0			10
WR268393										
BM00599	DD-I-49-B	100	14.6	P	F	F	23.0			10
WR268394										

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Inhibition F.B.S.[b]	Reactivation[c] GA	VX	GD	Dose	IN VIVO ASSAYS: Pretreatment 15 Min	Pretreatment 60 Min	Antidote
BM00606	DD-I-53-B	24					3.1			10
WR268395							12.5			0
							50			10
BM01238	DD-I-64	50					0.4	0	0	
WR268465							1.6	10	0	
							6.5	10	0	
BM01247	DD-I-69	>100	38	P	F	P	3	10	10	0
WR268466							12.2	50	40	20
							49	90	100	70
							62	30	40	
							250	30	70	
BM01694	JC-I-44-B	32					3.1	40	20	0
WR268500							12.5	10	10	10
							15.6	0	30	
							50.0	20	10	10
							62.5	30	10	
							250	30	10	
C. Phenoxymethyl Heteroaromatic Carbamataes										
1. Pyridinium Salts										
BM01256	DD-I-76-B	1.0	0.09	F	F	F	0.9	80	100	50
WR268467			396				3.5	60	100	60
							14	40	80	40
							15.6	90	90	
							62.5	100	90	
							250	80	30	
BM01265	DD-I-77-B	20	0.5	F	F	F	6.25	100	90	40
WR268468			11.9				15.6	90	90	
							25	80	90	30
							62.5	100	90	
							100	10	80	10
							250	100	90	
BM09332	DD-IV-16	0.052								

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Reactivation[c] F.B.S.[b]	GA	VX	GD	IN VIVO ASSAYS: Dose	Pretreatment 15 Min	Pretreatment 60 Min	Antidote
2. Imidazolium Salts										
BM01710	DD-I-82	12.6					1.25			40
WR268502							5.0			50
							20.0			60
BM01738	DD-I-87-B	0.125					0.007	60	40	30
WR268504							0.03	40	40	20
							0.11	30	50	10
BM03698	DD-II-61	>100								
BM09341	DD-IV-20	0.2								
3. Other Ring Systems										
BM02628	JC-I-64-B	2.0					3.1	20	50	
WR268567							17.3	60	50	
							49.0	30	70	
BM08657	DD-III-178	0.9								
BM09298	DD-III-193	0.1								
BM09305	DD-III-194A	0.8								
BM09314	DD-IV-10	0.2								
BM09323	DD-IV-15	1.2								

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Reactivation[c] F.B.S.[b]	GA	VX	GD	Dose	IN VIVO ASSAYS: Pretreatment 15 Min	Pretreatment 60 Min	Antidote
D. Imidazo[1,2-a] Pyridinium Salts										
BM02020	DD-J-98	17.1					5	80	90	30
WR268520							20	80	100	20
							80	10	60	0
BM02637	JC-I-71	19.5								
BM03198	JC-I-77	1.1					.62	80	50	0,10
WR258660							2.50	60	60	10,10
							10.0	30	40	30,70
BM03670	DD-II-34	4.5					2.2	50	60	20,10
WR268655							9.0	50	60	30,30
							36.0	70	30	40,40
BM03689	DD-II-45	2.5					3.1	50	60	30,40
WR268656							12.5	50	30	20,40
							50	30	20	30,10
BM04337	DD-II-75	1.6					6.25	30	30	20,30
WR268695							25.0	40	40	40,60
							100	20	60	50,50
BM04346	DD-II-104	1.1					0.8	10	40	70
WR268696							2.1	40	50	20,20
							3.1	20	30	90
							8.4			50,60
							12.4			10
							33.5			60,50
BM04355	DD-II-137	7.9					3.0	10	10	0,10
WR268697							11.9	30	0	90,20
							47.5	20	0	90,10
BM04364	DD-II-140	1.2					0.77	90	90	40,70
WR268699							3.10	70	70	60,90
							12.4	20	80	20,10

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Inhibition F.B.S.[b]	Reactivation[c] GA	VX	GD	IN VIVO ASSAYS: Dose	Pretreatment 15 Min	Pretreatment 60 Min	Antidote
BM04917	DD-II-162	42		P	P	F	3.1	60	60	0,10
WR268736							12.5	30	20	10,50
							50.0	20	60	0,20
BM04926	DD-II-163	0.2	0.2	F	F	F	3.1	50	50	10,30
WR268737			50.1				12.5	10	50	10,20
							50.0	10	10	10,0
BM04935	DD-II-178	1.35	0.6	F	F	F	2.1	60	80	80,20
WR268738			109.1				8.4	80	80	40,40
							33.5	10	50	70,40
BM05567	DD-III-1	24.5	66	P	P	P	6.2	60	70	60,60
WR268791							25	60	100	30,70
							100	50	80	70,60
BM05969	DD-III-24	4.0	0.5	F	F	F				
WR268823			25.8							
BM05978	DD-III-28	1.3	0.3	F	F	P				
WR268824			203.2							
BM05987	DD-III-29	0.35	0.1	F	F	F				
WR26826			2.3							
BM06475	DD-III-34	7.1								
BM06484	DD-III-36	10.0								
BM06493	DD-III-37									
BM06680	DD-III-49	24								
BM06699	DD-III-53									

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Reactivation[c] F.B.S.[b]	GA	VX	GD	IN VIVO ASSAYS: Dose	Pretreatment 15 Min	Antidote 60 Min
BM06706	DD-III-55								
BM07641	DD-III-61	12.6							
BM07650	DD-III-62								
BM07669	DD-III-100	12.6							
BM07678	DD-III-101								
BM07687	DD-III-112	33.6							
BM07696	DD-III-115	8.1							
BM07703	DD-III-117								
BM08611	DD-III-146								
BM08620	DD-III-147								
BM08639	DD-III-158	20.5							
E. Miscellaneous Compounds									
BM02646	JC-I-72-A						6.25	90	90
WR268569							25.0	90	100
							100	100	90

Bottle Number / WR Number	Our Sample Number	AChE IN VITRO ASSAYS: Inhibition Eel[a]	Reactivation[c] F.B.S.[b]	GA	VX	GD	IN VIVO ASSAYS: Dose	Pretreatment 15 Min	Pretreatment 60 Min	Antidote
BM03189 WR258297	DD-II-12	9.5					0.23	0	0	10
							1.0	0	0	0
							4.0	0	10	0
BM05950 WR268822	DD-III-18		15	P	F	F				
BM06500	DD-III-39	26.9								
BM08648	DD-III-174	50								

[a] IC_{50} in μM; under these conditions pyridostigmine has an IC_{50} of 0.6 μM.
[b] A single number represents per cent inhibition at 80μM. Two numbers = ID_{10} and ID_{90}.
[c] Pass or fail refers to 80μM.

Experimental Section

General Procedure for Synthesis of Phenoxymethyl Heteroaryl Ethers.

A solution of appropriate phenol (1.1 mol) and potassium hydroxide (2.5 mol) in DMSO (30 mL) was stirred at room temperature for 1 h. A solution of an appropriate chloride (picolyl chloride or 2-imidazolylmethyl chloride) in DMSO (20 mL) was then added in a dropwise manner. The reaction mixture was stirred at room temperature and poured into water (300 mL). The water layer was extracted with ethyl acetate (3x100 mL) and washed with water (3x100 mL), 10% sodium hydroxide solution (3x50 mL) and brine (3x50 mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and the residue was used for the next reaction without further purification. The following compounds were prepared by this method.

2-(Phenoxymethyl)pyridine was prepared from phenol in 70% yield.

2-[4'-(Methoxy)phenoxymethyl]pyridine was prepared from 4-methoxyphenol in 90% yield.

2-[(4-tert-Butyl)phenoxymethyl]pyridine was prepared from 4-*tert*-butylphenol in 75% yield.

2-[4'-(Formyl)phenoxymethyl]pyridine was prepared from 4-hydroxybenzaldehyde as described previously.<2>

2-[4'-(Carboxamido)phenoxymethyl]pyridine was prepared from 4-hydroxybenzamide in 87% yield. The reaction mixture was allowed to stir for 24 h.

2-[3'-(Formyl)phenoxymethyl]pyridine was prepared from 3-hydroxybenzaldehyde in 78% yield. The reaction mixture was allowed to stir for 24 h.

2-[4'-(Formyl)phenoxymethyl]imidazole was prepared in 54% yield from 4-hydroxybenzaldehyde. The reaction mixture was allowed to stir for 2.5 h.

2-[4'-(Carboxamido)phenoxymethyl]imidazole was prepared from 4-hydroxybenzamide in 29% yield. The reaction mixture was stirred for 4h.

2-[3'-(Formyl)phenoxymethyl]imidazole was prepared from 3-hydroxybenzaldehyde in 51% yield. The reaction mixture was allowed to stir for 2 h.

General Procedure for Synthesis of Quaternary Salts from Methyl p-Toluenesulfonate.

A solution of the appropriate phenoxy ethers and methyl p-toluenesulfonate (1.2-1.5 equiv) in anhydrous acetonitrile (45-50 mL) was refluxed for 60 h. The reaction mixture was cooled in an ice-water bath and the solid precipitate was filtered, washed with ether, dried and recrystallized with absolute ethanol and anhydrous ether. The following compounds were prepared by this method:

1-Methyl-2-[3'-(formyl)phenoxymethyl]pyridine p-Toluenesulfonate was prepared from 2-[4'-(formyl)phenoxymethyl]pyridine. The solid was recrystallized from ethanol and anhydrous ether to give the desired product in 57% yield.

1,3-Dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium p-Toluenesulfonate was prepared from 2-[4'-(formyl)phenoxymethyl)]-1-methylimidazole. The solid was recrystallized from ethanol and anhydrous ether to give the desired product in 69% yield.

1,3-Dimethyl-2-[3'-(formyl)phenoxymethyl]imidazolium p-Toluenesulfonate was prepared in a similar manner from 2-[3'-(formyl)phenoxymethyl]imidazole and used for the next reaction without further purification.

General Method for the Preparation of bis-Cationic Hydrazones.

A suspension (or a solution) of the appropriate quaternary salt (pyridinium, imidazolium, imidazo[1,2-a]pyridinium) (1.0 mmol) and an appropriate hydrazine (2-hydrazino-3,4,5,6-tetrahydropyrimidinium iodide or 2-hydrazinoimidazoline hydrobromide; 1.1 mmol) in absolute ethanol (50-200 mL) was refluxed for 6-7 h. The reaction mixture was cooled to room temperature and was then treated with conc HBr followed by stirring for 24-48 h. The solid formed was filtered, dried and recrystallized from an appropriate solvent.

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium Thiosemicarbazone Tosylate (BL58625; JP-I-17).

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate (1.0 g) was mixed with 0.25 g of thiosemicarbazide in absolute ethanol (20 mL). The mixture was heated to about 80° for one hour and it was then refrigerated. The product was collected by filtration and recrystallized from ethanol to give 1.07 g, mp 223-225°. The spectroscopic properties are consistent with expectation.

Anal. for $C_{22}H_{24}N_4O_4S_2$: C, 55.91; H, 5.12; N, 11.86; S, 13.57.
Found: C, 55.78; H, 5.14; N, 11.80; S, 13.49.

1-Methyl-2-(4'-formylphenylmethyl)pyridinium N',N'-Pentamethylenehydrazone Tosylate (BL58634; JP-I-20).

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate (1.0 g) and N-aminopiperidine (0.4 g) was dissolved in 10 mL of ethanol and refluxed three hours. The solution was reduced in volume by about one-half by rotary evaporation and chilled. Filtration gave 0.83 g (68%) of a solid which was recrystallized from absolute ethanol, mp 209-211. The spectroscopic properties are consistent with expectation.

Anal. for $C_{26}H_{31}N_3O_4S$: C, 64.84; H, 6.49; N, 8.73; S, 6.66.
Found: C, 65.09; H, 6.52; N, 8.81; S, 6.61.

1-Methyl-2-[4'-(methoxy)phenoxymethyl]pyridinium p-Toluenesulfonate (BM00188; DD-I-39-B).

This compound was prepared from 2-[4'-(methoxy)phenoxymethyl]pyridine as a crystalline solid in 85% yield: mp 150-152 °C; IR (KBr) 3460, 3080, 3000, 1630, 1600, 1500, 1440 cm^{-1}; ^1H (DMSOd_6, 300 MHz) 2.2 (s, 3H); 3.65 (s, 3H); 4.3 (s, 3H); 5.5 (s, 2H); 6.85 (d, 2H); 7.05 (t, 4H); 7.45 (d, 2H); 8.0 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1H); 9.05 (d, 1H).

Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.48; S, 7.98.
Found: C, 62.78; H, 5.82; N, 3.54; S, 7.99.

1-Methyl-2-(phenoxymethyl)pyridinium p-Toluenesulfonate (BM00197); DD-I-40-B).

This compound was prepared from 2-(phenoxymethyl)pyridine as a crystalline solid in 64% yield: mp 181-183 °C; IR (KBr) 3445, 3050, 3000, 1630, 1590, 1580 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) 2.2 (s, 3H); 4.3 (s, 3H); 5.55 (s, 2H); 7.05 (m, 3H); 7.25 (d, 2H); 7.3 (t, 2H); 7.45 (d, 2H); 8.05 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1H); 9.05 (d, 1H).

Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77; S, 8.63.
Found: C, 64.81; H, 5.78; N, 3.80; S, 8.71.

1-Methyl-2-[(4'-tert-butyl)phenoxymethyl]pyridinium p-Toluenesulfonate (BM00204; DD-I-41-B).

This compound was prepared from 2-[(4-tert-butyl)phenoxymethyl]pyridine as a white solid in 58% yield: mp 188-190 °C; IR (KBr) 3425, 3050, 2975,

1630, 1610, 1600, 1450 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) 1.2 (s, 12H); 2.25 (s, 3H); 4.3 (s, 3H); 5.55 (s, 3H); 7.05 (m, 4H); 7.3 (d, 2H); 7.45 (d, 2H); 8.05 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1H); 9.05 (d, 1H).

Anal. Calcd for: $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.28; S, 7.50.
Found: C, 67.60; H, 6.98; N, 3.39; S, 7.65.

1-Methyl-2-[4'-(formyl)phenoxymethyl]pyridinium N'-nicotinylhydrazone p-Toluenesulfonate (BM00213; DD-I-42).

A mixture of 2-[4'-(formyl)phenoxymethyl]pyridinium p-toluenesulfonate (4.0 g, 10 mmol) and nicotinic acid hydrazide (1.52 g, 11 mmol) was refluxed in absolute ethanol (105 mL) for 2 h. The reaction mixture was filtered hot to give 4.9 g (92%) of the desired product. The solid was recrystallized from methanol (300 mL) to give 4.3 g of analytically pure nicotinyl derivative: mp 261-263 °C; IR (KBr) 3275, 3065, 1680, 1653, 1608 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) 2.2 (s, 3H); 4.3 (s, 3H); 5.6 (s, 2H); 7.05 (d, 2H); 7.25 (d, 2H); 7.45 (d, 2H); 7.55 (d, 1H); 7.75 (d, 2H); 8.05 (t, 1H); 8.2 (d, 1H); 8.4 (s, 1H); 8.6 (t, 1H); 8.75 (d, 1H); 9.05 (m, 2H).

Anal. Calcd for $C_{27}H_{26}N_4O_5S$: C, 62.41; H, 5.24; N, 10.78; S, 6.17.
Found: C, 62.28; H, 5.18; N, 10.51; S, 6.52.

1-Methyl-2-[4'-(formyl)phenoxymethyl]pyridinium p-Toluenesulfonate (BM00571; DD-I-45-B).

This compound was prepared from 2-[4'-(formyl)phenoxymethyl]pyridine. The precipitated solid was recrystallized from acetonitrile in 63% yield: mp 199-200°; IR(KBr) 3130, 3100, 1730, 1640, 1620 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) δ2.2 (s, 3H); 4.4 (s, 3H); 5.6 (s, 2H); 7.0 (d, 2H); 7.2 (q, 4H); 7.8 (d, 2H); 8.05 (t, 1H); 8.1 (d, 1H); 8.6 (t, 1H); 9.0 (d, 1H); 9.9 (s, 1H).

Anal. Calcd for $C_{21}H_{21}NO_5S$: C, 63.13; H, 5.29; N, 3.50; S, 8.02
Found: C, 63.19; H, 5.32; N, 3.48; S, 8.10

1-Methyl-2-[(4'-(carboxamido)phenoxymethyl]pyridinium p-Toluenesulfonate (BM00580; DD-I-48-B).

This compound was prepared from 2-[(4-carboxamido)phenoxymethyl]pyridine. The solid obtained was recrystallized from methanol to give the desired product (77%): mp 249-250°C; IR(KBr) 3430, 3180, 3020, 1680, 1630, 1600, 1580 cm^{-1}; ^1H NMR (DMSO d_6, 300 MHz) 2.25d (s, 3H); 4.35 (s, 3H); 5.65 (s, 2H); 7.05 (d, 2H); 7.2 (d, 4H); 7.45 (d, 2H); 7.9 (d, 2H); 8.05 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1H); 9.05 (d, 1H).

Anal. Calcd for $C_{21}H_{22}N_2O_5S$: C, 60.85; H, 5.35; N, 6.76; S, 7.73
Found: C, 60.84; H, 5.36; N, 6.78; S, 7.77.

2-[4'-(N-Hydroxyiminomethyl)phenoxymethyl]pyridine.

A solution of 2-[4'-(formyl)phenoxymethyl]pyridine [3.0 g, 14.0 mmol) in ethanol (30 mL) was treated with a solution of hydroxylamine hydrochloride (1.06 g, 15.2 mmol) in water (10 mL). Sodium carbonate (2.39 g, 22.5 mmol) was added to the reaction mixture and the mixture was allowed to stir for 2 hrs. The precipitated solid was filtered and washed with water (3x50 mL), and recrystallized from ethanol and water to give 2.85 g of the desired oxime. mp 157-160°C.

1-Methyl-2-[4'-(N-hydroxyiminomethyl)phenoxymethyl]pyridinium p-Toluenesulfonate (BM00599; DD-I-49-B).

2-[4'-(N-Hydroxyimino)phenoxymethyl]pyridine was converted to the desired quaternary salt by the standard procedure. The solid was recrystallized from acetonitrile in 79% yield: mp 197-198°C; IR(KBr), 3480, 3180, 3080, 2980,

1630, 1600, 1520 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) δ 2.25 (s, 3H); 4.3 (s, 3H); 5.6 (s, 2H); 7.05 (d, 1H); 7.2 (d, 1H); 7.4 (d, 1H); 7.6 (d, 1H); 8.05 (m, 2H); 8.2 (d, 1H); 8.6 (t, 1H); 9.1 (d, 1H); 11.0 (s, 1H).

Anal. Calcd for $C_{21}H_{22}N_2O_5S$: C, 60.85; H, 5.35; N, 6.76, S, 7.73
Found: C, 60.89; H, 5.38; N, 6.79; S, 7.79

1,3-Dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium Thiosemicarbazone p-Toluenesulfonate (BM00606; DD-I-53-B).

A solution of 1,3-dimethyl-2-[4'-(formyl)phenoxymethyl)imidazolium p-toluenesulfonate (3.5 g, 8.8 mmol) and thiosemicarbazide (0.871 g, 9.5 mmol) was heated to reflux in absolute ethanol (80 mL) for 2h. The solution was cooled in an ice bath and treated with anhydrous ether. The solid obtained was filtered, dried and recrystallized with ethanol/ether to give 3.8 g (92%) of the desired product: mp 245-245°C; IR (kBr) 3420, 3300, 3170, 3120, 3000, 1600, 1500 cm^{-1}; H^1 NMR (DMSO-d_6) δ 2.25 (s, 3H); 3.9 (s, 6H); 5-5 (s, 2H); 7.1 (t, 44); 7.45 (d, 2H); 7.75 (m, 4H); 7.9 (br s, 1H); 8.0 (s, 1H); 8.25 (br s, 1H); 11.35 (s, 1H).

Anal. Calcd for $C_{21}H_{25}N_5S_2$: C, 53.05; H, 5.3; N, 14.73; S, 13.48
Found: C, 52.81; H, 5.34; N, 14.65; S, 13.40

2-[4'-(N-Hydroxyiminomethyl)phenoxymethyl]imidazole.

The title oxime was prepared from 2-[4'-(formyl)phenoxymethyl]imidazole in a similar manner as described previously for the pyridine analog.

1,3-Dimethyl-2-[4'-(N-hydroxyiminomethyl)phenoxymethyl]imidazolium p-Toluenesulfonate (BM01238; DD-I-64).

1-Methyl-2-[4'-(Hydroxyiminomethyl)-phenoxymethyl]imidazole was converted to the quaternary salt in the usual manner. The solid was recrystallized from ethanol and ether in 61% yield: mp 182-184°C; IR(KBr) 3460, 3180, 3100, 1500, 1200 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) δ 2.25 (s, 3H); 3.9 (s, 6H); 5.5 (s, 2H); 7.1 d(t, 4H); 7.45 (d, 2H); 7.55 (d, 2H); 7.75 (s, 2H); 8.1 (s, 1H); 11.05 (s, 1H).

Anal. Calcd for $C_{20}H_{23}N_3O_5S$: C, 57.53; H, 5.55; N, 10.06; S, 7.68
Found: C, 57.30; H, 5.60; N, 9.95; S, 7.55

1,3-Dimethyl-2-[4'-(carboxamido)phenoxymethyl]imidazolium p-Toluenesulfonate (BM01247; DD-I-69).

1-Methyl-2-[4'-(carboxamido)phenoxymethyl]imidazole was converted to the quaternary salt as described previously. The solid was crystallized from methanol to give the desired product in 61% yield: mp 255-257°C; IR(KBr) 3350, 3200, 3100, 1680, 1600, 1400 cm^{-1}; ^{1}HNMR (DMSOd_6, 300 MHz) δ 2.25 (s, 3H), 3.9 (s, 6H); 5.55 (s, 2H); 7.0-7.15 (m, 4H); 7.45 (d, 2H); 7.75 (s, 2H); 7.9 (d, 2H).

Anal. Calcd for $C_{20}H_{23}N_3O_5S$: C, 57.53; H, 5.55; N, 10.06; S, 7.67
Found: C, 57.50; H, 5.57; N, 10.05; S, 7.62

2-[4'-(Hydroxy)phenoxymethyl]pyridine.

A solution of hydroquinone (8.1 g, 73.5 mmol) in ethanol (30 mL) was added to a mixture of picolyl chloride hydrochloride (4.92 g, 29.9 mmol) and potassium hydroxide (1.68 g, 29.9 mmol) with stirring at room temperature. Potassium hydroxide (4.2 g, 74.8 mmol) was then added, and the reaction mixture was refluxed under an atmosphere of nitrogen for 24 h. The mixture was cooled and filtered, the solid washed with methanol (2x25 mL) and the combined filtrate and washings evaporated <u>in vacuo</u>. The gummy residue thus obtained was triturated with 10% sodium hydroxide (50 mL) and extracted with

ether (2x50 mL). The aqueous layer was acidified with concentrated hydrochloric acid (pH-7.0) and the precipitate filtered, washed with water and dried to give the desired phenoxymethyl ether. (4.4 g, 73%). This was used in the next reaction without further purification.

2-[4'-(N-Methylaminocarbonyloxy)phenoxymethyl]pyridine.

A solution of 2-[4'-(hydroxy)phenoxymethyl]pyridine (4.4 g, 21.8 mmol) in anhydrous tetrahydrofuran (50 mL) was treated with methyl isocyanate (13 mL). A small piece of sodium (~10 mg) was added to the solution and the mixture was allowed to stir at room temperature for 3.5 h. The mixture was filtered, the filtrate evaporated and the residue subjected to quaternization.

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]pyridine.

2-[4'-Hydroxy)-phenoxymethyl]pyridine (4.1 g, 20.3 mmol) was suspended in N,N-dimethylaminocarbamoyl chloride (30 mL). The reaction mixture was refluxed for 4 h, cooled to room temperature and poured onto ice water (100 mL). After the evolution of CO_2 ceased, the reaction mixture was basified with saturated sodium bicarbonate solution to pH 8.8. The solid was filtered, washed with water (2x100 mL) and dried. The crude product was then subjected to quaternization.

1-Methyl-2-[4'-N-(methylaminocarbonyloxy)phenoxymethyl]pyridinium p-Toluene sulfonate (BM01256; DD-I-76-B).

2-[4'-(N-methylaminocarbonyloxy)phenoxymethyl]pyridine was treated with methyl p-tosylate as described in the general procedure, to give a white precipitate. Recrystallization with 95% ethanol gave 76% of the desired salt: mp 209-210°C; IR(KBr) 3290, 3090, 3080, 3000, 2900, 1710, 1630, 1600 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.25 (s, 3H); 2.6 (d, 3H); 4.3 (s, 3H); 5.55 (s, 2H); 7.0-7.2 (m, 6H); 7.45 (d, 2H); 7.,55 (q, 1H); 8.05 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1); 9.05 (d, 1H).

Anal. Calcd for $C_{22}H_{24}N_2O_6S$: C, 59.44; H, 5.44; N, 6.30; S, 7.21
Found: C, 59.43; H, 5.47; N, 6.24; S, 7.26

1-Methyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl]pyridinium p-Toluenesulfonate (BM01265; DD-I-77-B).

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]pyridine was treated with methyl p-toluenesulfonate as described in the general procedure. Recrystallization with n-propanol gave 59% of the desired pyridinium salt: mp 193-195°C; IR(KBr) 3050, 3000, 2900, 1700, 1620, 1480 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) δ2.25 (s, 3H); 2.85 (s, 3H); 3.0 (s, 3H); 4.3 (s, 3H); 5.55 (s, 2H); 7.0-7.2 (s, 6H); 7.45 (d, 2H); 8.0 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1H); 9.1 (d, 1H).

Anal. Calcd for $C_{23}H_{26}N_2O_6S$: C, 60.24, H, 5.71; N, 6.11; S, 6.99
Found: C, 60.16; H, 5.71; N, 6.09; S, 6.92

1,3-Dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium N-(2-imidazolinyl)-hydrazone Dibromide (BM01274; JC-I-18-A).

1,3-Dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium p-toluenesulfonate was converted to the desired hydrazone by treatment with 2-hydrazino-imidazoline hydrobromide as described in the general procedure; mp 237-239°C; IR(KBr) 3400, 3150, 1660, 1600, 1500 cm^{-1}; ^1H NMR (DMSOd_6, 300 MHz) δ 3.7 (S, 4H); 3.9 (s, 6H); 5.6 (s, 2H); 7.2 (d, 2H); 7.85 (m, 3H); 8.15 (s, 1H).

Anal. Calcd for $C_{16}H_{22}N_6OBr_2 \cdot 1H_2O$: C, 39.03; H, 4.91; N, 17.01; Br, 32.46
Found: C, 39.14; H, 4.95; N, 17.06; Br, 32.39

1-Methyl-2-[4'-(formyl)phenoxymethyl]pyridinium S-Methylthiosemicarbonzone p-Toluensulfonate (BM01283; JC-I-19).

To a solution of 2-[4'-(formyl)phenoxymethyl]pyridinium p-tosylate (2.0 g, 5.0 mmol) in ethanol (30 mL) was added S-methyl thiosemicarbazide p-toluenesulonate (1.38 g, 5.0 mmol) and the reaction mixture was allowed to reflux for 24 h. The mixture was cooled in an ice water bath, the precipitate filtered and recrystallized from n-propanol to give 2.71 g (85%) of the desired thiosemicarbazone: mp 196-198°C; IR(KBr) 3550, 3100, 3070, 1630, 1600, 1510 cm^{-1}; ^1H NMR (DMSO d_6, 300 MHz) δ 2.2 (s, 6H); 2.7 (s, 3H); 4.3 (s, 3H); 5.65 (s, 2H); 7.1 (d, 4H); 7.3 d(d, 2H); 7.45 (d, 4H); 7.9 (d, 2H); 8.05 (t, 1H); 8.2 (d, 1H); 8.35d (s, 1H); 8.55 (t, 1H); 9.05 (d, 1H); 9.5 (br s, 1H).

Anal. Calcd for $C_{30}H_{34}N_4O_7S_3 \cdot 1H_2O$: C, 53.23; H, 5.36; N, 8.27; S, 14.21
Found: C, 53.21; H, 5.23; N, 8.09; S, 14.29

1,3-Dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium 3,4,5,6-tetrahydropyrmimid-2-ylhydrazone Dibromide (BM01292; JC-I-21-A).

1-Dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium tosylate was converted to the desired hydrazone by treatment with 2-hydrazino-3,4,5,6-tetrahydro-pyrimidinium iodide as described in the general procedure: mp 224-226°C; IR(KBr) 3400, 3250, 3200, 3150, 3050, 3000, 1650, 1630, 1500 cm^{-1}; ^1H NMR (DMSO d_6 300 MHz) δ 1.85 (m, 2H); 3.3 (m, 4H); 3.9 (s, 6H); 5.55 (s, 2H); 7.15 (d, 2H); 7.8-7.9 (t, 3H); 8.1 (s, 1H); 8.25 (br s, 1H).

Anal. Calcd for $C_{17}H_{24}N_6OBr_2.0.5H_2O$: C, 41.06; H, 5.03; N, 16.90; Br, 32.14
Found: C, 41.22; H, 5.18; N, 16.64; Br, 32.24

1-Methyl-2-[3'-(formyl)phenoxymethyl)pyridinium N-Methylthiosemicarbazone p-Toluenesulfonate.

A suspension of 1-methyl-2-[3'-(formyl)phenoxymethyl]-pyridinium p-toluenesulfonate (5.0 g, 12.5 mmol) in ethanol (150 ml) was treated with N-methylthiosemicarbazide (1.48 g, 14.0 mmol) and the reaction was refluxed for 6 h. The reaction mixture was then treated with conc HBr (15 mL) and stirred overnight. The mixture was filtered, dried and recrystallized from methanol to give 3.3 g (67%) of the desired semicarbazone: mp 241-242°C. IR(KBr) 3250, 3100, 2900, 1650, 1600 cm^{-1}4; ^1H NMR (DMSO d_6, 300 MHz) 2.9 (d, 3H); 4.35 (s, 3H); 5.65 (s, 2H); 7.2 (d, 2H); 7.8 (d, 2H); 7.95 (s, 1H); 8.15 (t, 1H); 8.2 (d, 1H); 8.45 (q, 1H); 8.6 (t, 1H); 9.1 (d, 1H).

Anal. Calcd for $C_{16}H_{19}N_4OSBr$: C, 48.61; H, 4.84; N, 14.17; Br, 20.21; S, 8.11
Found: C, 48.69; H, 4.87; N, 14.20; Br, 20.26; S, 8.13

1-Methyl-2-[3'-(formyl)phenoxymethyl]pyridinium N-(2-Imidazolinyl)hydrazone Dibromide (BM01701; JC-I-36-A)].

1-Methyl-2-[3'-(formyl)phenoxymethyl]pyridinium p-tosylate was converted to the hydrazone as described for the preparation of 1,3-dimethyl-2-[4'-(formyl)phenoxymethyl]imidazolium N-(2-imidazolinyl)hydrazone dibromide in 87% yield: mp 255°C; IR(KBr) 3510, 3420, 3320, 3200, 3170, 2950, 1670-1630, 1600, 1510 cm^{-1}; ^1H NMR (DMSO d_6 300 MHz) δ 3.5 (s, 4H); 4.4 (s, 3H); 5.7 (s, 2H); 7.25 (d, 1H); 7.35-7.5 (m, 2H); 7.5 (s, 1H); 8.05 (t, 1H); 8.15-8.25 (m, 2H); 8.6 (t, 1H); 9.1 (d, 1H).

Anal. Calcd for $C_{17}H_{21}N_5OBr_2$: C, 43.32; H, 4.49; N, 14.86; Br, 33.91
Found: C, 43.33; H, 4.52; N, 14.81; Br, 33.81

4-Hydroxyphenyl N,N-Dimethylcarbamate:

To a freshly prepared solution of sodium (2.87 g, 0.124 mmol) in 250 mL absolute ethanol (150 mL) under N_2 was dissolved hydroquinone (13.75 g, .124)

mol) followed by dropwise addition of dimethylcarbamoyl chloride (5.25 g, 0.048 mol) under stirring in a period of 30 min. The mixture was refluxed for 24 hrs, cooled, the precipitate was filtered off and the solvent evaporated *in vacuo*. The residue was triturated with 15% NaOH solution (50 mL) and extracted with ether (2x50 mL). The aqueous layer was acidified with conc hydrochloric acid and the precipitate was recrystallized from H_2O-ethanol to give off white crystals. (70% yield): mp 185°C.

3-Hydroxyphenyl N,N-Dimethylcarbamate.<8>

To a solution of resorcinol (15 g, 0.136 mol) and potassium hydroxide (7.6 g, .135 mol) in ethanol (200 mL) was added N,N-dimethylcarbamoyl chloride (5.8 g, 53 mmol) under stirring over a period of 30 min. The reaction mixture was refluxed for 24 hrs, cooled, the precipitate was filtered off and the solvent was evaporated *in vacuo*. The residue was triturated with 15% sodium hydroxide (50 mL), extracted with ether (2x50 mL), the aqueous layer was acidified with conc. HCl and the precipitate was recrystallized from benzene and hexane to give 59% of the desired monocarbamate: mp 98°C.

Alternative Procedures for Monocarbamoylation of Dihydroxbenzenes.

4-Hydroxyphenyl N,N-Dimethylcarbamate.

A suspension of hydroquinone (22 g, 0.2 mol) in xylene (600 mL) was heated to reflux and to this was added N,N-dimethylcarbamoyl chloride (24 mL 0.26 mol) dropwise over a period of 30 min. The reaction mixture was further refluxed for 4-5 h after the addition was complete. The reaction mixture was then cooled to room temperature and treated with ice cold sodium hydroxide solution (10%, 200 mL). The organic layer was separated and washed twice with 10% sodium hydride followed by water. All the aqueous extracts were combined and washed once with ether, and then acidified with 10% HCl to give a precipitate which was filtered and dried. The desired monocarbamate was thus obtained (15.0 g, 41%).

3-Hydroxyphenyl N,N-Dimethylcarbamate.

The compound was prepared from rescorcinol by the same procedure as described for the 4-isomer except that the aqueous layer was acidified and extracted with dichloromethane. The organic layer was then evaporated to give the desired monocarbamate (16.7 g, 46%).

2-Hydroxyphenyl N,N-Dimethylcarbamate.

The compound was prepared from catechol by the procedure and workup described for the 3-isomer and gave the desired product in 49% yield.

1-Methyl-2-[4'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]imidazole.

The title compound was prepared from 4-hydroxyphenyl N,N-dimethylcarbamate and 2-imidazoylmethyl chloride hydrochloride as described in the general procedure. The product was carried to next step without further purification.

1-Methyl-2-[3'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]pyridine.

The title compound was prepared from 3-hydroxyphenyl N,N-dimethyl carbamate and picolyl chloride hydrochloride as described in the general procedure. The product was carried to the next step without further purification.

1-Methyl-2-[3'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]imidazole.

This compound was prepared from 3-hydroxyphenyl N,N-dimethylcarbamate and 2-imidazoylmethyl chloride hydrochloride as described in the general

procedure. The product was carried to the next step without further purification.

1,3-Dimethyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl]imidazolium p-Toluenesulfonate (BM01710; DD-I-82).

This compound was prepared from 1-methyl-2-[4-(N,N-dimethylamino-carbonyloxy)phenoxymethyl]imidazole. Recrystallization from 95% ethanol afforded 71% of the desired salt: mp 218-220°C; IR (KBr) 3110, 3100, 3000, 2900, 1700, 1600, 1570 cm^{-1}; ^1H NMR δ 2.25 (s, 3H); 2.8 (s, 3H); 3.0 (s, 3H); 3.85 (s, 6H); 5.45 (s, 2H); 7.1 (m, 6H); 7.45 (d, 2H); 7.75 (s, 2H).

Anal. Calcd for $C_{22}H_{27}N_3O_6S$: C, 57.24; H, 5.89; N, 9.10; S, 6.94
Found: C, 57.34; H, 5.92; N, 9.10; S, 7.01

1-Methyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl]pyridinium p-Toluenesulfonate (BM01729; DD-I-86).

This compound was prepared 2-[3'-(N,N-dimethylaminocarbonyloxy)-phenoxymethyl]pyridine. Recrystallization from isopropanol afforded 76% of the desired salt: mp 155-156°C; IR(KBr) 3070, 3000, 2900, 1710, 1640, 1600, 1510 cm^{-1}; ^1H NMR ($DMSOd_6$, 300 MHz) δ 2.25 (s, 3H); 3.0 (s, 3H); 4.3 (s, 3H); 5.55 (s, 2H); 6.8 (d of d, 1H); 7.0-7.1 (m, 4H); 7.3 (t, 1H); 7.45 (d, 2H); 8.0 (t, 1H); 8.15 (d, 1H); 8.55 (t, 1H); ;9.1 (d, 1H).

Anal. Calcd for $C_{23}H_{26}N_2O_6S$: C, 60.24; H, 5.71; N, 6.11; S, 6.99
Found: C, 60.34; H, 5.71; N, 6.06; S, 7.06

1,3-Dimethyl-2-[3'-(N,N,-dimethylaminocarbonyloxy)phenoxymethyl]imidazolium p-Toluenesulfonate (BM01738; DD-I-87B).

This compound was prepared from 1-methyl-2-[(3-N,N-dimethylamino carbonyloxy)phenoxymethyl]imidazole. Recrystallization from 2-propanol afforded 52% of the desired salt: mp 113-115°C; IR(KBr) 3550, 3450, 3150, 3100, 3050, 2900, 1700, 1600, 1550, 1450 cm^{-1}; ^1H NMR ($DMSOd_6$, 300 MHz) δ 2.25 (s, 3H); 2.85 (s, 3H); 3.0 (s, 3H); 3.85 (s, 6H); 5.45 (s, 2H); 6.8 (d of d, 1H); 6.9 (m, 2H); 7.05-7.1 (d, 2H); 7.3 ;(t, 1H); 7.45 (d, 2H); 7.75 (s, 2H).

Anal. Calcd for $C_{22}H_{27}N_3O_6S \cdot 1H_2O$: C, 55.09; H, 6.09; N, 8.76; S, 6.68
Found: C, 55.37; H, 6.03; N, 8.74; S, 6.71

1-Methyl-2-[4'-(acetyl)phenxoymethyl]pyridinium N-(2-Imidazolinyl)hydrazone Dibromide (BM02002; DD-I-90).

1-Methyl-2-[4'-(acetyl)phenoxymethyl]pyridinium p-toluenesulfonate was converted to the desired hydrazone as described in the general procedure. The crude product was recrystallized from hot water in 46% yield: MP 271-272°C; IR (KBr) 3570; 3500, 3200, 1700, 1650, 1300 cm^{-1}; NMR ($DMSOd_6$) δ 2.25 (s, 3H); 3.7 (s, 4H); 4.35 (s, 3H); 5.65 (s, 2H); 7.2 (d, 2H); 7.95 (d, 2H); 8.1 (t, 1H); 8.2 (d, 1H); 8.6 (t, 1H); 9.1 (d, 1H).

Anal. Calcd for $C_{18}H_{23}N_5OBr_2$: C, 44.55; H, 4.77; N, 14.43; Br, 32.93
Found: C, 44.41; H, 4.84; N, 14.32; Br, 32.79.

1-Methyl-2-[4'-(Acetyl)phenoxymethyl]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide (BM02011; DD-I-90A).

1-Methyl-2-[4'-(acetyl)phenoxymethyl]pyridinium p-toluenesulfonate was converted to the desired hydrazone as described in the general procedure. The crude product was recrystallized from hot water in 66% yield: MP 276-278°C; IR (KBr) 3250, 1600, 1550, 1450, 1200 cm^{-1}; NMR (D_2O) δ 1.85 (m, 2H), 2.15 (s, 3H); 3.3 (m, 4H); 4.25 (s, 3H); 5.5 (s, 2H); 7.15 (d, 2H); 7.85 (d, 2H); 7.9 (t, 1H); 8.15 (d, 1H); 8.5 (t, 1H); 8.8 (d, 1H).

Anal. Calcd for $C_{19}H_{25}N_5OBr_2$: C, 45.70; H, 5.04; N, 14.02; Br, 32.01;
Found: C, 45.47; H, 5.11; N, 13.87; Br, 31.76.

General Procedure for the Synthesis of 6-Substituted-2-phenylimidazo[1,2-a]pyridines.

A mixture of the appropriate 5-substituted 2-aminopyridine (10 mmole) and an appropriately substituted phenacyl bromide (10 mmole) was refluxed in acetonitrile for 24 h. The solid obtained was then filtered and washed with acetone (2x50 mL) and dried. The hydrobromide salt of the imidazopyridine was then suspended in methanol/water (1:2, 100 mL) and neutralized with saturated sodium bicarbonate solution. The solid obtained was then filtered and washed with water (2x50 mL) and dried. The substituted imidazo[1,2-a]pyridine thus obtained was used for the next reaction without further purification.

General Procedures for Carbamoylation of Hydroxyphenylimidazopyridines.

Method A: A suspension of an appropriate hydroxyphenylimidazopyridine (10 mmol) in N,N-dimethylcarbamoyl chloride (30 mL) was heated at 120°C to reflux for 8-24 h. The reaction mixture was allowed to cool to room temperature and quenched with ice water. After all the carbon dioxide evolution had ceased, the mixture was neutralized with saturated sodium bicarbonate solution and the precipitate obtained was filtered and dried to give the desired carbamoylated product. The product was then subjected to quaternization without further purification.

Method B: A suspension or solution of an appropriate hydroxyphenyl imidazopyridine (10 mmol) in pyridine (20 mL) was treated with N,N-dimethylcarbamyl chloride (30 mmol). The reaction mixture was refluxed for 1-2 h and then poured into ice water and the precipitate obtained was filtered and dried to give the desired the carbamoylated product. The product obtained was quaternized without further purification.

General Procedure for the Preparation of N-Methylcarbamates.

A suspension of the appropriately substituted hydroxyphenyl imidazopyridine (1 mmol) in dry acetonitrile (50-100 mL) was treated with methyl isocyanate (10 equiv) and a catalytic amount of dibutyltin diacetate (2-3 drops). The reaction mixture was stirred for 24 h and filtered. The solid obtained was washed with ether and dried. The product was then subjected to quaternization without further purification.

General Procedure for Preparation of Quaternary Imidazo[1,2-a]pyridinium Iodides.

To a suspension or solution of an appropriate imidazopyridine in tetrahydrofuran (150 mL) was added iodomethane (large excess) the mixture was refluxed for 60 h. The precipitate obtained was filtered and washed with tetrahydrofuran and ether and dried to give the iodides. The products were recrystallized with acetonitrile/ether or ethyl acetate. In some cases the iodide salts were dissolved in methanol/acetonitrile and passed through an ion exchange column (Amberlite IRA 400 Cl^-). The solvent was then evaporated and the product obtained was then recrystallized from acetonitrile/ethyl acetate or ether to give the chloride salt of the appropriate imidazopyridines.

4-Hydroxy-α-bromoacetophenone.<9>

A solution of 4-hydroxyacetophenone (8.0 g, 59 mmol) in chloroform (50 mL) was added to a refluxing suspension of finely ground cupric bromide (22.2 g, 1.0 mol) in ethyl acetate (50 mL). The reaction mixture was refluxed with vigorous stirring for 1 h. The amber-colored suspension was then cooled to room temperature and filtered over Celite. The solid copper oxide was then washed several times with ethyl acetate (3 x20 mL). The solvent was evaporated *in vacuo* and the solid obtained was used as such for the next step.

2-[4'-Hydroxyphenyl]imidazo[1,2-a]pyridine.

A solution of 2-aminopyridine (5.96 g, 63.3 mmol) and α-bromo-4-hydroxyacetophenone (15.0 g, 69 mmol) in acetone (300 mL) was refluxed for 12-13 h. The solid obtained was filtered, dried and dissolved in hot water. The aqueous solution was then basified with saturated sodium bicarbonate solution until pH-7. The solid obtained was filtered, and washed several times with water and dried. The 2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine thus obtained was identified by NMR and used as such for the next step.

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine

2-(4'-Hydroxyphenyl)imidazo[1,2-a]pyridine (3.0 g, 14.2 mmol) was suspended in N,N-dimethylcarbamoyl chloride (30 mL). The reaction mixture was refluxed for 2 h, cooled to room temperature and poured into ice cooled water (100 mL). After the evolution of CO_2 ceased, the reaction mixture was basified with saturated sodium bicarbonate solution to pH 8.8. The solid was filtered, washed with water (2 x 100 mL) and dried (3.75g, 61%). The crude product was then subjected to quaternization.

1-Methyl-2-[4'-(N,N-dimethylaminocarbonyl)phenyl]imidazo[1,2-a]pyridinium p-Toluenesulfonate (BM02020; DD-I-98).

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine (3.7 g, 13 mmol) was treated with methyl p-toluenesulfonate (1 equiv) as described previously. Recrystallization with 95% ethanol gave 81% of the desired imidazo[1,2-a]pyridinium salt: MP: 193-194°C; IR (KBr) 3200, 3130, 3000, 1750, 1540, 1430 cm^{-1}; NMR (DMSOd_6) δ 2.2 (s, 3H); [illegible]9 (s, 3H); 3.05 (s, 3H); 3.9 (s, 3H); 7.05 (d, 2H); 7.35 (d, 2H); 7.45 (d, 2H); 7.55 (t, 1H); 7.76 (d, 2H); 8.05 (t, 1H); 8.25 (d, 1H); 8.55 (s, 1H); 8.9 (d, 1H).

Anal. Calcd for $C_{24}H_{25}N_3O_5S$: C, 61.65; H, 5.39; N, 8.98; S, 6.85;
Found: C, 61.52; H, 5.43; N, 8.93; S, 6.77.

1,3-Dimethyl-2-[3'-(formyl)phenoxymethyl]imidazolium N-(2-Imidazolinyl) hydrazone Dibromide (BM02039; JC-I-44-A).

1,3-Dimethyl-2-[3'-(formyl)phenoxymethyl]imidazolium p-toluenesulfonate was converted to the hydrazone as described in the general procedure. The product was crystallized and recrystallized from 95% ethanol and ethyl acetate in 62% yield: MP 243°C; IR (KBr) 3300, 3150, 1600, 1450 cm^{-1}; NMR (DMSOd_6) δ 3.7 (s, 4H); 3.9 (s, 6H); 5.6 (s, 2H); 7.15 (d, 1H); 7.45 (m, 2H); 7.65 (s, 1H); 7.8 (s, 2H); 8.15 (s, 1H).

Anal. Calcd for $C_{16}H_{22}N_6OBr_2 \cdot 1\ H_2O$: C, 39.03; H, 4.91; N, 17.01; Br, 32.46;
Found: C, 38.94; H, 4.96; N, 16.97; Br, 32.36.

1-Methyl-2-[4'-(formyl)phenoxymethyl]imidazo[1,2-a]pyridinium N-(2-Imidazolinyl\hydrazone Dibromide (BM02048; JC-I-59).

1-Methyl-2-[4'-(formyl)phenoxymethyl]imidazo[1,2-a]pyridinium p-toluenesulfonate was converted to the hydrazone as described above. The crude product was crystallized from methanol in 56% yield: MP 285-286°C; IR (KBr) 3500, 3300, 1700, 1680, 1640, 1550 cm^{-1}; NMR (DMSOd_6) δ 3.7 (s, 4H); 4.05 (s, 3H); 5.6 (s, 2H); 7.2 (d, 2H); 7.55 (t, 1H); 7.8 (d, 2H); 8.05 (t, 1H); 8.15 (s, 1H); 8.25 (d, 1H); 8.55 (s, 1H); 8.95 (d, 1H).

Anal. Calcd for $C_{19}H_2N_6OBr_2 \cdot 1H_2O$: C, 43.20; H, 4.57; N, 15.90; Br, 30.24;
Found: C, 43.18; H, 4.65; N, 15.80; Br, 30.34.

Preparation of 2-Chloromethylimidazo[1,2-a]pyridine.

A solution of 2-aminopyridine (20 g, 0.21 mol) and 1,3-dichloroacetone (25.4 g, 0.201 mol) in reagent grade acetone was refluxed for 24 h. The

reaction mixture was cooled and the precipitated solid was filtered, washed with water and dried. The solid was then acidified with dilute HCl and refluxed for 1 h. The solution was cooled and neutralized with saturated sodium bicarbonate solution. The precipitated solid was filtered, dried and recrystallized from ethanol to give 16.4 g (50%) of the desired 2-chloromethylimidazo[1,2-a]pyridine.

Preparation of 2-[4'-(formyl)phenoxymethyl]imidazo[1,2-a]pyridine.

A solution of 4-hydroxybenzaldehyde (7.9 g, 64 mmol) and 2-chloromethyl imidazo[1,2-a]pyridine (8.0, 48 mmol) in ethanol (60 mL) was refluxed in the presence of potassium hydroxide (4.2 g, 74.8 mmol) for 5 h. The reaction mixture was quenched with water (500 mL). The precipitate obtained (9.1 g, 75%) was filtered, dried, and used for the next step without further purification.

1-Methyl-2-[3'-(formyl)phenoxymethyl]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide (BM02057; JC-I-63).

1-Methyl-2-[3'-(formyl)phenoxymethyl]pyridinium p-toluenesulfonate was converted to the desired hydrazone as described in the general procedure. The crude product was crystallized from 95% ethanol and ethyl acetate in 91% yield: MP 245-247°C; IR (KBr) 3400, 3200, 3000, 2800, 1640, 1600, 1410 cm^{-1}; NMR (DMSO$\underline{d}_6$) δ 1.85 (m, 2H); 3.3 (m, 4H); 4.4 (s, 3H); 5.7 (s, 2H); 7.25 (d, 1H); 7.4 (t, 1H); 7.5 (d, 1H); 7.8 (s, 1H); 8.05 (t, 1H); 8.15 (s, 1H); 8.2 (d, 1H); 8.35 (s, 2H); 8.6 (t, 1H); 9.1 (d, 1H).

Anal. Calcd for $C_{18}H_{23}N_5OBr_2$: C, 44.55; H, 4.77; N, 14.43; Br, 32.93;
Found: C, 44.35; H, 4.86; N, 14.25; Br, 32.73.

1,3-Dimethyl-2-[3'-(formyl)phenoxymethyl]imidazolium 3,4,5,6 Tetrahydropyrimid-2-ylhydrazone Dibromide (BM02600; JC-I-34-B).

1,3-Dimethyl-2-[3'-(formyl)phenoxymethyl]imidazolium p-toluenesulfonate was converted to the desired hydrazone as described in the general procedure. The crude product was recrystallized from 95% ethanol in 72% yield: MP, 247-248°C; IR (KBr) 3250, 3150, 3000, 1630, 1600 cm^{-1}; NMR (DMSO $\underline{d}_6$) δ 1.85 (m, 2H); 3.3 (m, 4H); 3.9 (s, 6H); 5.6 (s, 2H); 7.15 (d, 1H); 7.4 (t, 1H); 7.5 (d, 1H); 7.7 (s, 1H); 7.8 (s, 2H); 8.15 (s, 1H); 8.3 (br s; 2H).

Anal. Calcd for $C_{17}H_{24}N_6OBr_2$; C, 41.81; H, 4.95; N, 17.21; Br, 32.73;
Found: C, 41.71; H, 4.97; N, 17.11; Br, 32.63.

1-Methyl-2-[4'-(formyl)phenoxymethyl]imidazo[1,2-a]pyridinum 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide (BM02619; JC-I-58).

1-Methyl-2-[4'-(formyl)phenoxymethyl]imidazo[1,2-a]pyridinium p-toluenesulfonate was converted to the desired hydrazone as described in the general procedure. The crude product was crystallized from 95% ethanol in 88% yield: MP 293°C; IR (KBr) 3350, 3250, 1640, 1600, 1500, 1470 cm^{-1}; NMR (DMSO$\underline{d}_6$) δ 1.8 (m, 2H); 3.3 (m, 4H); 4.05 (s, 3H); 5.6 (s, 2H); 7.2 (d, 2H); 7.55 (t, 1H); 7.85 (d, 2H); 8.15 (t, 1H); 8.1 (s, 1H); 8.25 (m, 3H); 8.6 (s, 1H); 8.95 (d, 1H).

Anal. Calcd for $C_{20}H_{24}N_6OBr_2 \cdot 1\ H_2O$: C, 44.30; H, 4.83; N, 15.49; Br, 29.47;
Found: C, 44.61; H, 5.02; N, 15.58; Br, 29.76.

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]imidazo[1,2-a]pyridine.

To a solution of 4-hydroxyphenyl N,N-dimethylcarbamate (4.73 g, 26.0 mmol) in DMSO (25 mL) was added potassium hydroxide (1.33 g, 23.7 mmol) and the mixture was stirred at room temperature for 1 h. A solution of 2-chloromethylimidazo[1,2-a]pyridine (3.49 g, 20.0 mmol) in DMSO (25 mL) was added to the reaction mixture and the mixture was stirred for an additional 4 h. The

reaction mixture was then quenched with water (200 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was repeatedly washed with water (3 x 50 mL), brine (50 mL) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* resulted in the crude carbamate which was used for the next step without further purification.

1-Methyl-2-[4'-(N,N-Dimethylaminocarbamyloxy)phenoxymethyl]imidazo[1,2-a]pyridinium p-Toluenesulfonate (BM02628; JC-I-64-B).

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]imidazo[1,2-a]pyridine was treated with methyl p-toluenesulfonate as described in the general procedure. The crude product obtained was crystallized from isopropanol in 68% yield: MP: 175-176°C IR (KBr) 3400, 3100, 3000, 2850, 1680, 1620, 1550 cm^{-1}; NMR ($DMSOd_6$) δ 2.2 (s, 3H); 2.85 (s, 3H); 2.95 (s, 3H); 4.0 (s, 3H); 5.5 (s, 2H); 7.1 (m, 6H); 7.4 (d, 2H); 7.5 (t, 1H); 8.0 (t, 1H); 8.2 (d, 1H); 8.5 (s, 1H); 8.9 (d, 1H).

Anal. Calcd for $C_{25}H_{27}N_3O_6S$: C, 60.34; H, 5.47; N, 8.44; S, 6.44;
Found: C, 60.33; H, 5.50; N, 8.37; S, 6.38.

2-[4'-(N-Methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

A suspension of 2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine (3.6 g, 17 mmol) in anhydrous tetrahydrofuran (100 mL) was treated with catalytic amount of sodium (5 piece ~20-30 mg) and the mixture was allowed to stir for 5 min. A solution of methyl isocyanate (3.4 mL, 3.2 q, 57 mmol) in anhydrous THF (10 mL) was added to the suspension and the mixture was allowed to stir for 3 h (until all the solid went into solution). The mixture was filtered and the solvent evaporated to give the desired the carbamate. The product was confirmed by NMR and subjected to quaternization using methyl iodide.*

*Methyl tosylate resulted in an unseparable mixture of products.

1-Methyl-2-[4'-(N-Methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Iodide (BM02637; JC-I-71).

2-[4'-(N-Methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine (5.0 g, 18.0 mmol) was suspended in THF (100 mL) and treated with iodomethane (15 mL). The mixture was refluxed for 3 days and the solid obtained was filtered, washed with anhydrous ether (3 x 25 mL). The crude product was crystallized from acetonitrile/ethyl acetate to give (4.9 g, 69%) of imidazo[1,2-a]pyridinium salt: mp: 190-192°C; IR (KBr) 3200, 3000, 1700, 1600, 1500, 1450 cm^{-1}; NMR ($DMSOd_6$) δ 2.65 (d, 3H); 3.95 (s, 3H); 7.35 (d, 2H); 7.55 (t, 1H); 7.7 (m, 3H); 8.05 (t, 1H); 8.25 (d, 1H); 8.55 (s, 1H); 8.95 (d, 1H).

Anal. Calcd for $C_{16}H_{16}N_3O_2I$: C, 46.96; H, 3.94; N, 10.26; I, 31.01;
Found: C, 47.03; H, 3.98; N, 10.20; I, 31.09.

1-Methyl-2-[(N-methylaminocarbonyloxy)methyl]imidazole.

A solution of 1-methyl-2-hydroxymethylimidazole<10> (5.0 g, 44 mmol) in dichloromethane (50 mL) was treated with methyl isocyanate (11 mL). Dibutyl tindiacetate (2-3 drops) were then added and the mixture was stirred at room temperature for 5 h. The solvent was then removed *in vacuo* and the solid obtained was triturated with ether and filtered to get 5.75 g (76%) of the desired carbamate. The carbamate was quaternized without further purification.

1,3-Dimethyl-2-[(N-Methylaminocarbonyloxy)methyl]imidazolium iodide (BM02646; JC-I-72-A).

1-Methyl-2-[(N-methylaminocarbonyloxy)methyl]imidazole was methylated with iodomethane. The product was recrystallized with isopropanol in 51% yield: MP: 159-161°C; IR (KBr) 3200, 3000, 2960, 1680, 1480 cm^{-1}; NMR

(DMSOd_6) δ 2.5 (d, 3H); 3.85 (s, 6H); 5.3 (s, 2H); 7.4 (m, 1H); 7.7 (s, 2H).

Anal. Calcd for $C_8H_{14}N_3O_2I$: C, 30.88; H, 4.53; N, 13.50; I, 40.79;
Found: C, 30.98; H, 4.56; N, 13.44; I, 40.82.

6-Nitro-2-phenylimidazo[1,2-a]pyridine.

A solution of phenacyl bromide (10.0 g, 50 mmol) and 5-nitro-2-aminopyridine (6.9 g, 49.6 mmol) in acetonitrile (100 mL) was refluxed fo 24 h. The solid obtained was filtered and washed with acetone. Usual workup (as described for 2-(4-hydroxyphenyl)imidazo[1,2-a]pyridine) gave the desired imidazopyridine in 75% yield. The product was identified by NMR and used for the next reaction.

6-Amino-2-phenylimidazo[1,2-a]pyridine.

To a mixture of 6-nitro-2-phenylimidazo[1,2-a]pyridine (2.5 g, 10.0 mmol) and Pd/C (10%, 0.206 g) in ethanol (50 mL) was added a solution of sodium hypohosphite (5 g, 56 mmol) in water (50 mL). The mixture was refluxed for 1.5 h, filtered through Celite and the residue was washed with water. The combined filtrate and washings were then cooled in ice and neutralized with saturated sodium bicarbonate solution. The amine that precipitated out was filtered, dried to give the amine in 87.5% yield. The product was characterized by NMR and used for the next step.

6-Acetamido-2-phenylimidazo[1,2-a]pyridine.

A suspension of the above amine (5.2 g, 24.8 mmol) in acetic anhydride (45 mL) was stirred at 70-80°C for 15 min. After all the solid had dissolved the solution was cooled in ice and filtered. The residue was washed with ether until free of acetic anhydride and dissolved in a minimum amount of hot methanol followed by neutralization with saturated sodium bicarbonate solution. The precipitate obtained was filtered, and dried to give the desired acetamidoimidazopyridine (5.4 g, 87 yield). The product was identified by NMR and used for the next step without further purification.

1-Methyl-6-acetamido-2-phenylimidazo[1,2-a]pyridinium Iodide (BM03189; DD-II-12).

6-Acetamido-2-phenylimidazo[1,2-a]pyridine was quaternized with iodomethane. The product was recrystallized from methanol to give 77% of the desired quaternary iodide: MP: 178-181°C; IR (KBr) 3400, 3120, 3100, 3000, 1660, 1500, cm^{-1}; NMR (DMSOd_6) δ 2.1 (s, 3H); 3.7 (s, 3H); 7.65 (m, 5H); 7.85 (d, 1H); 8.25 (d, 1H); 8.65 (s, 1H); 9.55 (s, 1H); 10.55 (s, 1H).

Anal. Calcd for $C_{16}H_{16}N_3OI$: C, 48.86; H, 4.10; N, 10.68; I, 32.27;
Found: C, 48.93; H, 4.13; N, 10.64; I, 32.30.

6-Nitro-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 5-nitro-2-aminopyridine (8.3 g, 59 mmol) and α-bromo 4-hydroxyacetophenone (12.9 g, 60 mmol) in acetonitrile (100 mL) was refluxed for 24 h. The solid obtained was filtered, dried and neutralized with satd $NaHCO_3$ solution. The precipitate obtained was filtered, dried and the product (72%) identified by NMR to be the desired 6-nitroimidazopyridine.

6-Amino-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

The above 6-nitroimidazopyridine (2.5 g, 9.9 mmol) was converted to the title compound by the procedure described for the unsubstituted phenyl analog. The desired product was obtained in 89% yield and was identified by NMR. The product was used for the next step without further purification.

6-Acetamido-2-(4'-acetoxyphenyl)imidazo[1,2-a]pyridinium Acetate.

A suspension of the above amine (2.6 g, 11.5 mmol) in acetic anhydride (15 mL) was heated for 10 min. After all the solid had dissolved, the solution was cooled in an ice bath and the precipitated solid was filtered and washed with anhydrous ether until free of acetic anhydride. The crude product was identified as a triacetate (2.8 g, 66%) by NMR and subjected to hydrolysis.

6-Acetamido-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

To a suspension of 6-acetamido-2-(4'-acetoxyphenyl)imidazo[1,2-a]pyridine (2.8 g, 7.5 mmol) in methanol (100 mL) was added a solution of sodium bicarbonate (1.4 g, 16.6 mmol) in water (15 mL). The mixture was refluxed for 30 min during which all the solid dissolved. The solution was concentrated in vacuo and the solid obtained was filtered, washed with water and dried to give 1.9 g (95%) of the desired amide.

6-Acetamido-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Acetamido-2-[4'-hydroxyphenyl]imidazo[1,2-a]pyridine was converted to the desired carbamate as described previously. The product was identified by NMR and was obtained in 94% yield. The carbamate was quaternized without further purification.

1-Methyl-6-acetamido-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium iodide (BM03198; JC-I-77).

The title compound was prepared by treating the acetamido carbamate with methyl iodide. Recrystallization from methanol gave the desired quaternary carbamate in 66% yield: MP: 302-304°C; IR (KBr) 3400, 3250, 3000, 1720, 1650, 1550, 1500, 1460 cm^{-1}; NMR ($DMSO\underline{d}_6$) δ 2.1 (s, 3H); 2.65 (d, 3H); 3.9 (s, 3H); 7.35 (d, 2H); 7.65 (d, 2H); 7.75 (m, 1H); 7.8 (d, 1H); 8.25 (d, 1H); 8.65 (s, 1H); 9.6 (s, 1H); 10.55 (br s, 1H).

Anal Calcd for $C_{18}H_{19}N_4O_3I$: C, 46.37; H, 4.11; N, 12.02; I, 27.22;
Found: C, 46.10; H, 4.17; N, 11.89; I, 27.01.

6-Nitro-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 2-amino-5-nitropyridine (7.9 g, 56.7 mmol) and 3'-hydroxy-α-bromoacetophenone (12.34 g, 57.3 mmol) was heated to reflux in acetonitrile (100 mL) for 24 h. The precipitate was filtered, washed with acetone and dried. The solid obtained was dissolved in hot 10% sodium hydroxide solution (100 mL), filtered, cooled in ice and acidified with acetic acid to pH7. The precipitate obtained was filtered, dried (65% yield) and used for the next step. The compound was characterized by NMR.

6-Nitro-2-(3'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

A mixture of 6-nitro-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine (3.0 g, 11.0 mmol) and N,N-dimethylcarbamoyl chloride (20 mL) was refluxed for 6 h. The solution was quenched with ice cold water and the solid obtained (after the evolution of carbon dioxide had ceased) was filtered, dried (64% yield). The compound was characterized by NMR, and used for the next step.

6-Amino-2-(3'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

A suspension of the above 6-nitro imidazopyridine carbamate (2.1 g, 6.4 mmol), 10% Pd/C (0.21 g) and a solution sodium hypophosphite (4.2 g, 39.6 mmol) in water (41 mL), was heated to reflux in ethanol (95%, 41 mL) for 1-1.5 h. The mixture was filtered through celite and the residue washed with water. The combined filtrate was cooled and neutralized with saturated sodium bicarbonate solution and then extracted with ethyl acetate. The organic layer

was further washed with water, brine, dried (Na_2SO_4) and evaporated *in vacuo* to get a solid in 78% yield. The compound was characterized by NMR and used for the next step.

6-Acetamido-2-(3'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

6-Amino-2-(3'-N,N,dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine (5.29 g, 17.8 mmol) was heated in acetic anhydride (10 mL) or acetic anhydride:acetic acid mixture (1:1) for 45 min. The solution was cooled in ice and the solid was precipated by addition of THF. The precipitate was filtered, washed several times with ether and dried. The solid was dissolved in methanol and neutralized with saturated sodium bicarbonate solution. The mixture was diluted with water (50 mL) and the solid obtained was filtered and dried (86%) yield).

1-Methyl-6-acetamido-2-(3'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridinium p-Toluenesulfonate. [DD-II-45; BM03689].

6-Acetamido-2-(3'-N,N-dimethylcarbonyloxyphenyl)imidazo[1,2-a]pyridine (5.75 g, 16.9 mL) was treated with methyl p-toluenesulfonate (3.3 g, 17.0 mmol) in THF (160 mL). The mixture was heated to reflux for 3 days and the solid obtained was filtered, dried and crystallized and recrystallized from acetonitrile/ether to give 2.7 g (35%) of the desired product: mp 190°-192°C; IR (KBr) 3450, 1700, 1550, 1360 cm^{-1}; H^1 NMR (DMSO-d_6) δ 2.1 (s, 3H); 2.25 (s, 3H); 2.9 (s, 3H); 3.05 (s, 3H); 3.9 (s, 3H); 7.05 (d, 2H); 7.3-7.7 (m, 6H) 7.85 (d, 1H); 8.2 (d, 1H); 8.65 (s, 1H); 9.55 (s, 1H); 10.6 (s, 1H).

Anal. calcd for $C_{26}H_{28}N_4O_6S$: C, 59.52; H, 5.37; N, 10.68; S, 6.11.
Found: C, 59.62; H, 5.39; N, 10.65; S, 6.17.

6-Amino-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

6-Nitro2-(3'-hydroxiphenyl)imidazo[1,2-a]pyridine (5.0 g, 19.5 mmol) was reduced with sodium hypophosphite and Pd/C as described for the 4'-isomer except that the solid obtained after neutralization was filtered and dried (78% yield). The product was used for the next step without further purification.

6-Acetamido-2-(3'-acetoxyphenyl)imidazo[1,2-a]pyridinium Acetate.

6-Amino-2-(3'-hydroxyphenyl)imidazo([1,2-a]pyridine (3.9 g, 17.3 mmol) was heated in acetic anhydride (30 mL) until all the solid dissolved and the solution was cooled in ice and treated with ether to give the solid that was filtered and washed with ether and dried to give the acetate (66% yield).

6-Acetamido-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of the acetate salt (8.0 g, 21.6 mmol) in methanol (40 mL) was treated with a solution of sodium bicarbonate (4.0 g, 47.6 mmol) in water (50 mL). The mixture was refluxed for 15 min, cooled to room temperature and the solid obtained was filtered to give the desired product in 93% yield.

6-Acetamido-2-[3'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

To a suspension of 6-acetamido-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine (2.9 g, 10 mmol) in THF (200 mL) was added sodium (5-6 pieces ≈30mg). The mixture was stirred for 5 min and treated with methyl isocyanate (3 mL, 58 mmol) and the suspension was allowed to stir overnight and filtered. The solid was washed with ether and dried to give the desired product in 62% yield.

1-Methyl-6-acetamido-2-(3'-N-methylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridinium iodide. [DD-II-34; BM03670].

A suspension of 6-acetamido-2-(3'-N-methylaminocarbonyloxyphenyl)-imidazo[1,2-a]pyridine (5.0 g, 15.4 mmol) in THF (200 mL) was treated with a large excess of iodomethane and the mixture was refluxed for 3 days. The solid obtained was filtered and crystallized from acetonitrile to give the desired salt in 50% yield: mp 253-255°C; IR (KBr) 3400-3300, 3100, 1720, 1700, 1650, 1530 cm^{-1}; H^1 NMR (DMSO-d_6) δ 2.15 (s, 3H); 2.65 (d, 3H); 3.9 (s, 3H); 7.0 (m, 1H); 7.3-7.5 (m, 2H); 7.6 (t, 1H); 7.7 (q, 1H); 7.8 (d, 1H)' 8.7 (s, 1H); 9.6 (s, 1H); 10.6 (s, 1H).

Anal. calcd for $C_{18}H_{19}N_4O_3I$: C, 46.37; H, 4.11; N, 12.01; I, 27.22.
Found: C, 46.39; H, 4.12; N, 11.91; I, 27.14.

5-Hydroxy-2-(p-nitrophenylazo)pyridine.

To a solution of p-nitroaniline (7.4 g, 53.5 mmol) in hydrochloric acid (60 mL, 1 part of water and 1 part of conc HCl) was added an ice cold solution of sodium nitrite (5.5 g, 79.7 mmol) in water (12 mL). The addition was done at such a rate that the temperature of the reaction mixture was maintained at -5°C. The diazonium chloride solution was then added to a cold solution of 3-hydroxypyridine (5.0 g, 52.5 mmol) and sodium hydroxide (2.1 g, 52.5 mmol) in water (100 mL), with a simultaneous addition of 10% sodium hydroxide (100 mL) in such a way that the pH of the reaction mixture was maintained close to neutral. After stirring for an additional hour the mixture was acidified with glacial acetic acid, filtered and dried. The solid obtained was a mixture of two isomers and the mixture was used without crystallization for the next step.

5-Benzoyloxy-2-(p-nitrophenylazo)pyridine.

To a solution of the above azo dye (mixture of isomers) (5.46 g, 22.3 mmol) and potassium carbonate (6.1 g, 44.0 mmol) in water (150 mL) was added benzoyl chloride (3.8 mL, 32.7 mmol) at room temperature. The mixture was stirred for 1 hour and the precipitate obtained was filtered, and washed thoroughly with water, dried and crystallized from benzene to give 5.2 g (67%) of the desired 5-benzoyloxy-2-(p-nitrophenylazo)pyridine. The compound was characterized by NMR.

2-Amino-5-benzoyloxypyridine.

To a suspension of 5-benzoyloxy-2-(p-nitrophenylazo)pyridine (9.5 g, 27.2 mmol) and 10%-Pd/C (0.490 g) in ethanol (250 mL) was added a solution of sodium hypophosphite (20.7 g, 195 mmol) in water (125 mL). The reaction mixture was heated to reflux for 1.5 h and filtered through Celite. The residue was washed with water and the combined filtrate was cooled and neutralized with saturated sodium bicarbonate solution. The crystalline solid obtained was filtered and dried to give 4.5 g (77%) of the amine.

6-Hydroxy-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 2-amino-5-benzoyloxypyridine (4.5 g, 21.0 mmol) and 4-hydroxy-α-bromoacetophenone (5.85 g, 27.2 mmol) in acetone (75 mL) was heated to reflux for 24 h. The precipitate was filtered, washed with acetone and dried. The solid was then dissolved in 10% sodium hydroxide solution (100 mL) and warmed to 40-50°C. The solution was cooled and acidified with glacial acetic acid to pH 7 to give a solid which was filtered, washed with water and dried. The product was identified by NMR and used for the next step.

6-N,N-Dimethylaminocarbonyloxy-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)-imidazo[1,2-a]pyridine.

A suspension of 6-hydroxy-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine (4.1

g, 18.1 mmol) in N,N-dimethylcarbamoyl chloride (10 mL) was heated to reflux for 4 h. The reaction mixture was worked up as described in the general procedure to give the desired bis-carbamate (5.00 g, 75%). The product was identified by NMR and subjected to quaternization.

1-Methyl-6-(N,N-dimethylaminocarbonyloxy)-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridinium chloride. [DD-II-75; BM04337].

The title compound was prepared treating the bis-carbamate with methyl iodide as described in the general procedure, followed by passage through an ion exchange resin. The desired product was obtained in 87% yield after recrystallization from isopropanol and ethyl acetate: mp 219-220°C; IR (KBr) 3400, 2900, 1700, 1450, 1430, 1350 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.87 (s, 3H); 2.9 (s, 3H); 3.05 (s, 3H); 3.1 (s, 3H); 3.9 (s, 3H); 7.35 (d, 2H); 7.7 (d, 2H); 8.05 (d, 1H); ;8.35 (d, 1H); 8.65 (s, 1H); 9.1 (s, 1H).

Anal. calcd for $C_{20}H_{23}N_4O_4Cl \cdot 0.5_2O$: C, 56.13; H, 5.65; N, 13.09; Cl, 8.28.
Found: C, 56.29; H, 5.67; N, 13.17; Cl, 8.20.

6-Acetamido-2-(4'-morpholinocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

A suspension of 6-acetamido-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine (2.3 g, 8.6 mmol), potassium carbonate (5.4 g, 39.0 mmol) and morpholinocarbonyl chloride (5.9 mL, 7.56 g, 50.5 mmol) in acetonitrile (100 mL) was heated to refluxed for 3 days. The mixture was then poured into 5% sodium hydroxide solution (200 mL) and filtered. The solid was dried and washed with 5% NaOH solution (25mL), water (2x25 mL) and dried to give the desired morpholinocarbamate (2.45 g, 75%). The product was identified by NMR and subjected to quaterization.

1-Methyl-2-acetamido-2-(4'-morpholinocarbonyloxyphenyl)imidazo[1,2-a]pyridinium chloride. [DD-II-137; BM04355].

The above acetamido carbamate (4.4 g, 11.5 mmol) was subjected to quaternization followed by ion exchange as described in the general procedure to give 77% of the desired salt. After recrystallization with ethanol and ether: mp 287-288°C; IR (KBr) 3400, 3010, 2950, 1710, 1650, 1540, 1500 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.15 (s, 3H); 3.4 (m, 2H); 3.6 (m, 6 H); 3.9 (s, 3H); 7.4 (d, 2H); 7.7 (d, 2H); 8.05 (d, 1H); 8.25 (d, 1H); 8.65 (s, 1H); 9.6 (s, 1H).

Anal. calcd for $C_{21}H_{23}N_4O_4Cl$: C, 58.53; H, 5.37; N, 13.00; Cl, 8.22.
Found: C, 58.25; H, 5.46; N, 12.91; Cl, 8.15.

6-Formamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

Acetic-formic anhydride was generated by dropwise addition of 96% formic acid (1.90 mL, 49.5 mmol) to acetic anhydride (3.68 mL, 39.0 mmol) at 0°C. The mixture was then heated at 50-60°C for 2 h and cooled to room temperature followed by addition of THF (10 mL). A suspension of the 6-amino imidazo[1,2-a]pyridine intermediate (4.4 g, 14.8 mmol) in THF (100 mL) was added to the mixed anhydride at 0°C and the reaction mixture was allowed to stir overnight at room temperature. The volatiles were removed in vacuo. The solid obtained was triturated with ether and filtered. The crude N-formyl derivative was then dissolved in hot ethanol (95%) and neutralized with saturated sodium bicarbonate solution. The mixture was further diluted with water and the precipitate obtained was filtered and dried to give 4.5 g (93%) of the desired product. The product was identified by NMR.

1-Methyl-6-formamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridinium chloride. [DD-II-140; BM04364].

6-Formamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine was quaternized in the usual manner followed by ion exchange and recrystallization of the chloride salt from methanol and ether to give 76% of

the desired product: mp 278°C; IR (KBr) 3400, 2900, 1690, 1650, 1540, 1500, cm^{-1} ^1H NMR (DMSOd_6) δ 2.9 (s, 3H); 3.05 (s, 3H); 3.9 (s, 3H); 7.4 (d, 2H); 7.7 (d, 2H); 7.9 (d, 2H); 8.25 (d, 2 H); 8.4 (s, 1H); 8.65d (s, 1H); ;9.6 (s, 1H).

Anal. calcd for $C_{18}H_{19}N_4O_3Cl$: C, 57.67; H, 5.10; N, 14.94; Cl, 9.45.
Found: C, 57.57; H, 5.13; N, 14.84; Cl, 9.49.

1-Methyl-2-(N,N-dimethylaminocarbonyloxymethyl)imidazole.

A solution of 1-methyl-2-hydroxymethylimidazole (5.0 g, 44.5 mmol) triethylamine (5.5 mL, 5.4 g, 53.3 mmol) and N,N-dimethylcarbamoyl chloride (4.9 mL, 5.7 g, 53.0 mmol) in THF (100 mL) was refluxed for 24 h. The volatiles were removed in vacuo and the residue was dissolved in CH_2Cl_2 (50 mL) and extracted with water. The organic layer was washed with water (25 mL) brine (25 mL) dried (Na_2SO_4) and evaporated in vacuo. The oil obtained (5.6 g, 69%) was characterized by NMR and subjected to quaternization.

1,3-Dimethyl-2-(N,N-dimethylaminocarbonyloxymethyl)imidazolium p-Toluenesulfonate. [DD-II-61; BM03698].

A solution 1-methyl-2-(N,N-dimethylaminocarbonyloxymethyl)imidazole (5.6 g, 30.5 mmol) and methyl p-toluenesulfonate (5.5 g, 29.5 mmol) in acetonitrile (50 mL) was refluxed for 60 h. The solid obtained was filtered and then recrystallized from acetonitrile and ether to give 8.4 g (76%) of the desired salt: mp 151-153°C; IR (KBr) 1680, 1470, 1380, 1150 cm^{-1}; ^1H NMR (DMSOd_6) δ 2.25 (s, 3H); 2.8 (s, 3H); 2.85 (s, 3H); 3.9 (s, 3H); 5.3 (s, 2H); 7.05 (d, 2H); 7.45 (d, 2H); 7.5 (s, 2H).

Anal. calcd for $C_{16}H_{23}N_3O_5S$: C, 52.02; H, 6.27; N, 11.37, S, 8.66
Found: C, 52.12; H, 6.29; N, 11.41; S, 8.56.

6-Nitro-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

To a suspension of 6-nitro-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine (20 g, 78 mmol) in pyridine (100 mL) was added N,N-dimethylcarbamoyl chloride (26 mL, 280 mmol) and the mixture was refluxed for 1.5 h. The solution was then quenched with ice water and the solid obtained was filtered, washed with water and dried to give the desired carbamate in 92% yield. The product obtained was characterized by NMR and used for the next step.

6-Amino-2-(4'-N,N-dimethylcarbonyloxyphenyl)imidazo[1,2-a]pyridine.

A suspension of the 6-nitroimidazopyridine carbamate (19.5 g, 71.5 mmol), 10% Pd/C (1.1g) and a solution of sodium hypophosphite (28 g, 358.2 mmol) in water (175 mL) was heated to reflux in 95% ethanol (350 mL) for 1-1.5h. The mixture was filtered through Celite and the residue washed with water. The filtrate was combined, cooled and neutralized with saturated sodium bicarbonate solution and then extracted with ethyl acetate. The organic layer was further washed with water, brine, dried (Na_2SO_4) and evaporated in vacuo to get a solid (15.8 g, 89%). The compound was characterized by NMR and used for the next step.

6-Methoxycarbonylamino-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

To an ice cold suspension of 6-amino-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine (6.4 g, 21.5 mmol) and sodium carbonate (22.4 g, 107 mmol) in THF and water (1:1), 1200 mL) was added a solution methyl chloroformate (7 ml, 8.54 g, 9.0 mmol) in THF (10 mL) in a dropwise manner. The reaction mixture was vigorously stirred for 30 min and concentrated in vacuo. The solution was cooled and quenched with a large excess of water. The solid that precipitated was filtered and dried to give 67% of the desired carbamate.

1-Methyl-6-(methoxycarbonylamino)-2-(4'-N,N-dimethylcarbonyloxyphenyl) imidazo[1,2-a]pyridinium chloride. [DD-II-104; BM04346]

6-Methoxycarbonylamino-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo-[1,2-a]pyridine(4.4 g, 12.3 mmol) was treated with methyl iodide as described in the general procedure. The solid obtained was dissolved in acetonitrile (200 mL) and passed through an ion exchange (Amberlite IRA 400 Cl) column. The solvent was evaporated and the solid obtained was recrystallized with isopropanol/ether to give the desired salt in 68% yield: mp 213-214°C; IR (KBr) 3400, 1700, 1550, 1500, 1460 cm^{-1}; H^1 NMR (DMSO-d_6) δ 2.9 (s, 3H); 3.5 (s, 3H); 3.7 (s, 3H); 3.9 (s, 3H); 7.35 (d, 2H); 7.95 (d, 1H); 8.25 (d, 1H); 8.65 (s, 1H); 9.25 (s, 1H).

Anal. calcd for $C_{19}H_{21}N_4O_4Cl$: C, 56.36; H, 5.22; N, 13.84; Cl, 8.75.
Found: C, 56.16; H, 5.29; N, 13.66; Cl, 8.67.

6-Benzamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

A suspension of the aminoimidazopyridine intermediate (4.0 g, 13.5 mmol) in acetone (25 mL) and sodium carbonate solution (3.21 g, 30 mmol) in water (30 mL) was cooled in an ice bath. Benzoyl chloride (3.1 mL, 26.7 mmol) was added in a dropwise manner. The mixture was stirred for 15 min, filtered and washed with water. The solid was dried (5.0 g, 92%) and characterized by NMR and subjected to quaternization.

1-Methyl-6-benzamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridinium chloride [DD-II-163;BM04926].

The 6-benzamidoimidazopyridine intermediate (4.6 g, 11.4 mmol) was treated with methyl p-toluenesulfonate (4.46 g, 23.9 mmol) in THF (200 mL). The mixture was heated to reflux for 3 days and the solid obtained was filtered, washed with THF followed by ether, and dried. The solid was dissolved in methanol and acetonitrile (1:1, 100 mL) and passed through an ion exchange resin (amberlite, IRA-400 Cl^-)). The solvent was evaporated *in vacuo* and the solid obtained was crystallized with anhydrous ethanol and ether to give 3.4 g (66%) of the desired chloride salt mp 280-282°C; IR (KBr) 3450, 3050, 1760, 1680, 1500, 1400 cm^{-1}; H^1 NMR (DMSOd_6) δ 2.9, (s, 3H); 3.05 (s, 3H); 3.9 (s, 3H); 7.4 (d, 2H); 7.5-7.65 (m, 3H), 7.7 (d, 2H); 8.05 (d, 2H); 8.3 (d, 2H); 8.7 (s, 1H); 9.8 (s, 1H).

Anal. calcd for $C_{24}H_{23}N_4O_3Cl$: C, 63.92; H, 5.14; N, 12.42; Cl, 7.86.
Found: C, 63.86; H, 5.19; N, 12.33; Cl, 7.96

6-Sulfonamido-2-[4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

To a suspension of the 6-aminoimidazopyridine intermediate (4.0 g, 13.5 mmol) in pyridine (40 mL), cooled to 0°C was added methanesulfonyl chloride (1.614 mL, 20.8 mmol) in a dropwise manner. The reaction mixture was stirred at room temperature for 1 h and quenched with water. The solid obtained was filtered and dried to get the desired product (3.5 g, 70%). The product was characterized by NMR and subjected to quaternization.

1-Methyl-6-methanesulfonamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)-imidazo[1,2-a]pyridinium chloride. [DD-II-162; BM04917].

A suspension of the 6-methanesulfonamidoimidazopyridine intermediate (4.0 g, 10.0 mmol) and methyl p-toluenesulfonate (3.4 g, 18 mmol) in THF (200 mL) was heated to reflux for 3 days. The solid obtained was filtered and washed with tetrahydrofuran and dried. The solid was then dissolved in a methanol/acetonitrile mixture and passed through an ion exchange column (Amberlite IRA-400 Cl^-). The solvent was evaporated *in vacuo* and the solid obtained was recrystallized from anhydrous ethanol/ether to give the desired chloride salt: mp 235-238°C, IR (KBr) 3400, 3150, 3080, 1720, 1500, 1400 cm^{-1}; ^1H NMR (DMSOd_6) δ 2.9 (d, 3H); 3.05 (d, 3H); 3.1 (s, 1.5 H); 3.15 (s, 1.5 H); 3.9 (s,

3H); 7.25 (d, 1H); 7.4 (d, 2H); 7.7 (d, 2H); 7.85 (d, 1H); 7.9 (d, 1H); 8.25 (d, 1H); 8.6 (s, 1H); 8.8 (s, 1H).

Anal. calcd for $C_{18}H_{21}N_4O_4SCl$: C, 50.87; H, 4.98; N, 13.18; S, 7.54; Cl, 8.34.
Found: C, 50.69; H, 4.95; N, 13.14; S, 7.63; Cl, 8.27.

6-(N-Methylureido)-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

To a suspension of the 6-aminoimidazopyridine intermediate (4.9 g, 16.20 mmol) in acetone (100 mL) was added methyl isocyanate (3.4 mL, 57 mmol). The reaction mixture was stirred for 24 h at room temperature and filtered. The solid obtained was washed with ether to give 4.5 g (77%) of the urea. The compound was characterized by NMR and then quaternized.

1-Methyl-6-(N-methylureido)-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo-[1,2-a]pyridinium chloride. [DD-II-178; BM04935].

The 6-(N-methylureido)imidazopyridine intermediate was quaternized and subjected to ion exchange as described in the general procedure to give 67% of the desired imidazopyridinium salt: mp 255-257°C; IR (KBr) 3320, 3120, 3000, 1780, 1700, 1580 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.65 (d, 3H); 2.9 (s, 3H); 3.05 (s, 3H); 3.9 (s, 3H); 6.7 (q, 1H); 7.35 (d, 2H); 7.65 (d, 2H); 7.8 (d, 1H); 8.15 (d, 1H); 8.55 (s, 1H); 9.3 (s, 1H).

Anal. calcd for $C_{19}H_{22}N_5O_3Cl$: C, 56.50; H, 5.49; N, 17.34; Cl, 8.77.
Found: C, 56.48; H, 5.53; N, 17.25; Cl, 8.79.

6-Formamido-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

Acetic-formic anhydride was generated by dropwise addition of 96% formic acid (2.7 mL, 70.3 mmol) to acetic anhydride (5 mL, 52.9 mmol) at 0°C. The mixture was then heated at 50-60°C for 2 h and cooled to room temperature, followed by addition of THF (10 mL). A suspension of the 6-aminoimidazopyridine intermediate (6.0 g, 20 mmol) in THF (150 mL) was added to the mixed anhydride and the reaction mixture was allowed to stir overnight at room temperature. The volatiles were removed <u>in vacuo</u>, the solid obtained was tritruated with ether and filtered. The crude N-formyl derivative was then dissolved in hot 95% ethanol and neutralized with saturated sodium bicarbonate solution. The mixture was then diluted with water and the precipitate obtained was filtered and dried to give 5.7 g (87%) of formamido derivative. The compound was characterized by NMR and subjected to reduction.

6-Methylamino-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

To a suspension of the above 6-formamidoimidazopyridine intermediate (5.7 g, 17.6 mmol) in THF (100 mL) was added a solution of $BH_3 \cdot THF$ (50 mL) in a dropwise manner. The temperature was maintained at 0°C throughout the addition. After the addition was complete, the mixture was heated to reflux for 1 h. The reaction mixture was poured very carefully into ice cold water and the precipitate obtained was filtered and dried to give 5.3 g (98%) of the desired product. The product was characterized by NMR and then acetylated.

6-(N-Methylacetamido)-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)imidazo[1,2-a]pyridine.

A solution of the above N-methylaminoimidazopyridine intermediate (5.0 g, 16.1 mmol) in pyridine (50 mL) was treated with acetic anhydride (10 mL) and the mixture was stirred for 24 h at room temperature. The reaction mixture was evaporated <u>in vacuo</u> and the residue was triturated with ether. The solid obtained was filtered and washed with ether and dried. The crude acetamido derivative was triturated with water, filtered, and dried to give the desired product (4.6 g, 80%). The product was subjected to quaternization without further purification.

1-Methyl-6-(N-methylacetamido)-2-(4'-N,N-dimethylaminocarbonyloxyphenyl)-imidazo[1,2-a]pyridine chloride. [DD-III-1; BM05567].

A suspension of the 6-(N-methylacetamido)imidazopyridine intermediate (4.0 g, 11.0 mmol) in THF (100 mL) was treated with iodomethane (25 mL) and the mixture was refluxed for 3 days. The compound was converted to the chloride salt by ion exchange and crystallized from acetonitrile/ethyl acetate to give 3.0 g (66%) of the desired salt: mp 229-230°C; IR (KBr) 3020, 2980, 1695, 1640, 1510 cm^{-1} ^1H NMR (D_2O) (major and minor conformer) δ 1.9 (s, 3H); 2.3 (s, 3H); 3.0 (s, 3H); 3.1 (s, 3H); 3.3 (s, 3H); 3.5 (s, 3H); 4.0 (d, 3H); 7.35 (d, 2H); 7.7 (d, 2H); 7.9-8.15 (m, 2H); 8.2 (s, 1H); 8.25 (s 1H); 8.8 (s, 1H); 8.9 (s, 1H).

Anal. calcd for $C_{20}H_{23}N_4O_3Cl$: C, 59.62; H, 5.75; N, 13.90; Cl, 8.79.
Found: C, 59.52; H, 5.76; N, 13.95; Cl, 8.72.

2-Ethoxycarbonylimidazo[1,2-a]pyridine.

Following the general procedure for imidazopyridine synthesis, a mixture of ethyl α-bromopyrurate and 2-aminopyridine were refluxed to give 61% of the desired imidazopyridine.

6-Methyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

5-Methyl-2-aminopyridine was refluxed with α-bromo-4-hydroxyacetophenone to give the desired methyl substituted imidazopyridine in 79% yield.

2-(3'-Hydroxyphenyl)imidazo[1,2-a]pyridine.

A mixture of 2-aminopyridine was refluxed along with 3-hydroxy-α-bromoacetophenone to give the desired product in 77% yield.

6-Trifluoromethyl-2-[3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 5-trifluoromethyl-2-aminopyridine and 3'-hydroxy-α-bromoacetophenone were refluxed to give 6-trifluoromethyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine in 90% yield.

6-Trifluoromethyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

5-Trifluoromethyl-2-aminopyridine was refluxed along with 4-hydroxy-α-bromoacetophenone to give the desired product in 83% yield.

6-Chloro-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 5-chloro-2-aminopyridine and 3'-hydroxy-α-bromoacetophenone were refluxed to give the desired imidazopyridine in 82% yield.

6-Chloro-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

5-Chloro-2-aminopyridine was refluxed along with 4 hydroxy-α-bromo-acetophenone to give the desired product in 81% yield.

6-Methyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

5-Methyl-2-aminopyridine was refluxed along with 3 hydroxy-α-bromo-acetophenone to give the desired product in 73% yield.

2-(N-methylaminocarbonyloxymethyl)imidazo[1,2-a]pyridine.

Ethyl imidazopyridine-2-carboxylate (5.7 g, 29.9 mmol) was dissolved in THF (7.5 mL) and added dropwise to a suspension of lithium aluminum hydride (0.68 g, 44.2 mmol) in THF (75 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The reaction

mixture was quenched by sequential addition of water (1.68 mL), 15% sodium hydroxide solution (1.68 mL) and water (5.04 mL) and stirred for 1 h. The suspension was filtered and the residue was washed with hot ethyl acetate. The filtrate and the washings were mixed, dried (Na_2SO_4) and evaporated to dryness. The alcohol obtained was then carbamoylated according to the general procedure to give 57% of the desired carbamate.

1-Methyl-2-[(N-methylaminocarbonyloxy)methyl]imidazo[1,2-a]pyridinium Iodide. [DD-III-18; BM05950]

A suspension of the above imidazopyridine carbamate (4.9 g, 23 mmol) was quaternized and crystallized from acetonitrile/ethylacetate to give 6.2 g (69%) of the desired iodide, mp 197-198°C. IR (KBr) 3300, 3100, 1720, 1500, 1200 cm^{-1}; ^1H NMR ($DMSO_{d_6}$) δ 2.55 (d, 3H); 3.95 (s, 3H); 5.32 (s, 2H); 7.25 (q, 1H); 7.5 (t, 1H); 8.0 (t, 1H); 8.2 (d, 1H); 8.4 (s, 1H); 8.9 (d, 1H).

Anal. Calcd for $C_{11}H_{14}N_3O_2I$: C, 38.05; H, 4.06; N, 12.10; I, 36.55.
Found: C, 38.11; H, 4.10; N, 12.05; I, 36.61.

6-Methyl-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Methyl-2-[4'-hydroxyphenyl]imidazo[1,2-a]pyridine was converted to the desired carbamate by the general procedure in 69% yield.

1-Methyl-6-methyl-2-[4'-(N-methylaminocarbamyloxy)phenyl]imidazo[1,2-a]pyridinium iodide. [DD-III-24; BM05969]

6-Methylimidazo[1,2-a]pyridine carbamate (5.0 g, 17.0 mmol) was quaternized and recrystallized from acetonitrile/ether to give 6.6 g (87%) of the desired iodide salt: mp 168-173°C; IR (KBr) 3300, 3000, 1720, 1500, 1200 cm^{-1}; ^1H NMR ($DMSO_{d_6}$) δ 2.4 (s, 3H); 2.65 (d, 3H); 3.9 (s, 3H); 7.35 (d, 2H); 7.65-7.8 (m, 3H); 7.95 (d, 1H); 8.2 (d, 1H); 8.5 (s, 1H); 8.75 (s, 1H).

Anal. Calcd for $C_{17}H_{18}N_3O_2I$: C, 48.24; H, 4.28; N, 9.92; I, 29.98.
Found: C, 48.35; H, 4.30; N, 9.94; I, 29.88.

6-Methyl-2-[4'-(N,N-dimethylaminocarbanyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Methyl-2-[4'-hydroxyphenyl]imidazopyridine was converted to N,N-dimethyl carbamate by the general procedure in 57% yield.

1-Methyl-6-methyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium chloride. [DD-III-28; BM05978].

The above dimethylcarbamate (3.7 g; 12.5 mmol) was quaternized and worked up as usual. The compound was dissolved in a mixture of acetonitrile and methanol (1:1) and passed through an ion exchange (Cl^-) column. The eluent was then evaporated to dryness and the residue crystallized from acetonitrile/ethyl acetate to give 4.0 g (90%) of the desired salt: mp 210-212°C; IR (KBr) 3500, 3100, 1720, 1600, 1500, cm^{-1}; ^1H NMR ($DMSO_{d_6}$) δ 2.4 (s, 3H); 2.9 (s, 3H); 3.05 (s, 3H); 3.95 (s, 3H); 7.35 (d, 2H); 7.7 (d, 2H); 7.9 (d, 1H); 8.25 (d, 1H); 8.6 (s, 1H); 8.85 (s, 1H).

Anal. Calcd for $C_{18}H_{20}N_3O_2Cl \cdot 0.5H_2O$: C, 60.92; H, 5.96; N, 11.84; Cl, 9.99.
Found: C, 60-76; H, 6.09; N, 11.73; Cl, 9.89.

2-[3'-(N-Methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

2-(3'-Hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the N-methyl carbamate in 73% yield by the general procedure.

1-Methyl-2-[3'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Iodide. [DD-III-29; BM05987].

The carbamate (3.8 g, 14.2 mmol) was quaternized and crystallized from acetonitrile to give 4.9 g (83%) of the desired product: mp 125-127°C, IR (KBr) 7.35 (d, 1H); 7.45-7.65 (m, 4H); 7.75 (q, 1H); 8.05 (t, 1H); 8.3 (d, 1H); 8.6 (s, 1H); 8.9 (d, 1H).

Anal. Calcd for $C_{16}H_{16}N_3O_2I \cdot 0.5H_2O$: C, 45.94; H, 4.09; N, 10.04; I, 30.34.
Found: C, 45.90; H, 4.08; N, 10.08; I, 30.37.

2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl)]imidazo[1,2-a]pyridine.

2-(3'-Hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired dimethyl carbamate in 55% yieldby the general procedure.

1-Methyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Chloride. [DD-III-34; BM06475].

The imidazo[1,2-a]pyridine carbamate (3.3 g, 11.7 mmol) was quaternized, converted to the chloride and recrystallized as described in the general procedure to give 3.3 g (84%) of the chloride salt: mp 241-243°C; IR (KBr) 3500, 3100, 1720, 1650, 1500, 1400 cm^{-1}; ^1H NMR (D_2O) δ 3.0 (s, 3H); 3.15 (s, 3H); 3.45 (s, 3H); 7.35 (d, 1H), 7.4 (s, 1H); 7.5 (m, 1H); 7.65 (t, 1H); 8.0 (m, 2H), 8.25 (s, 1H); 8.7 (d, 1H).

Anal Calcd for $C_{17}H_{18}N_3O_2Cl \cdot 0.25H_2O$: C, 60.71; H, 5.54; N, 12.50, Cl, 10.54.
Found: C, 60.89; H, 5.42; N, 12.53; Cl, 10.51.

6-Nitroimidazo[1,2-a]pyridine.

A mixture of 2-amino-5-nitropyridine (4.6 g, 33.0 mmol), α-bromo-acetaldehyde diethylacetal (6.55 g, 33.0 mmol) and pyridinium p-toluenesulfonate (4.0 g, 15 mmole) in acetonitrile (50 mL) was heated for 24 h. The mixture was worked up as described in the general procedure to give 4.4 g (83%) of the desired imidazopyridine. The product obtained was carried to the next step.

6-Acetamidoimidazo[1,2-a]pyridine.

6-Nitroimidazopyridine (5.0 g, 30.g mmol) was suspended in methanol (250 mL) and hydrogenated at 40 psi for 6 h. The solution obtained was filtered through Celite and evaporated to dryness and the product obtained was (3.3 g, 82%), warmed with acetic anhydride (40 mL). The solid obtained was filtered and dissolved in water and neutralized with sodium bicarbonate solution. The precipitate obtained was then filtered and dried (4.1 g, 95%). The compound was subjected to quaternization without further purification.

1-Methyl-6-acetamidoimidazo[1,2-a]pyridinium Iodide. [DD-III-39; BM06500].

The above 6-acetamidoimidazopyridine intermediate (2.4 g, 13.6 mmol) was quaternized and recrystallized from ethanol to give 3.1 g (72%) of the desired salt: mp 294-296°C; IR (KBr) 3000, 1680, 1500, 1300 cm^{-1}; ^1H NMR (D_2O) δ 2.2 (s, 3H); 4.0 (s, 3H); 7.8-7.95 (m, 3H); 8.05 (s, 1H); 9.2 (s, 1H).

Anal. Calcd for $C_{10}H_{12}N_3OI$: C, 37.87; H, 3.81; N, 13.25; I, 40.01.
Found: C, 37.92; H, 3.83; N, 13.18; I, 39.93.

6-Trifluoromethyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Trifluoromethyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the dimethylcarbamate in 69% yield by the general procedure.

1-Methyl-6-trifluoromethyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenyl]-imidazo[1,2-a]pyridinium Chloride. [DD-III-36; BM06484].

The above 6-trifluoromethylimidazopyridine dimethylcarbamate (5.0 g, 13.6 mmol) was quaternized, converted to the chloride and crystallized from acetonitrile/ethyl acetate to give 5.0 g (89%) of the desired product: mp 243-245°C; IR (KBr) 3400, 3000, 1720, 1400, 1350 cm^{-1}; ^1H NMR ($DMSOd_6$)δ 2.9 (s, 3H); 3.05 (s, 3H); 4.0 (s, 3H), 7.4 (d, 2H); 7.7 (d, 2H); 8.4 (d, 1H); 8.55 (d, 1H); 8.7 (s, 1H); 9.75 (s, 1H).

Anal. Calcd for $C_{18}H_{17}N_3O_2F_3Cl\cdot 1.0H_2O$: C, 51.74; H, 4.58; N, 10.05; Cl, 8.48.
Found: C, 51.56; H, 4.60; N, 9.97; Cl, 8.39.

6-Trifluoromethyl-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Trifluoromethyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate in 65% yield by the general procedure.

1-Methyl-6-trifluoromethyl-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Chloride. [DD-III-37; BM06493].

The 6-trifluoromethylimidazo[1,2-a]pyridine carbamate (5.0 g, 14.9 mmol) was quaternized, converted to the chloride and recrystallized from acetonitrile/ethyl acetate to give 4.5 g (78%) of the desired product: mp 305-308°C; IR (KBr) 3500, 3100, 1710, 1680, 1500, 1320 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.7 (d, 3H), 4.0 (s, 3H); 7.35 (d, 2H); 7.7 (d, 2H); 7.8 (q, 1H); 8.4 (d, 1H); 8.55 (d, 1H); 8.65 (s, 1H); 9.7 (s, 1H).

Anal. Calcd for $C_{17}H_{15}N_3O_2F_3Cl\cdot 0.5H_2O$: C, 51.71; H, 4.08; N, 10.64; Cl, 8.94;
Found: C, 51.66; H, 4.10; N, 10.61; Cl, 8.92.

6-Methyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Methyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted the dimethyl carbamate in 51% yield by the general procedure.

1-Methyl-6-methyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Iodide Chloride. [D-III-49; BM06680].

6-Methylimidazopyridine carbamate intermediate (3.5 g, 11.8 mmol) was quaternized, converted to the chloride and recrystallized from acetonitrile/ethyl acetate to give 3.4 g (85%) of the desired salt: mp 208-210°C; IR (KBr) 3400, 3000-3100, 1710, 1400, 1200 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.4 (s, 3H); 2.9 (s, 3H); 3.05 (s, 3H); 3.95 (s, 3H); 7.35 (d, 1H); 7.5-7.65 (m, 3H); 7.9 (d, 1H); 8.2 (d, 1H); 8.55 (s, 1H); 8.8 (s, 1H).

Anal. Calcd for $C_{18}H_{20}N_3O_2Cl\cdot 0.75H_2O$: C, 60.16; H, 5.82; N, 11.69; Cl, 9.87;
Found: C, 60.10; H, 5.98; N, 11.75; Cl, 9.77.

6-Methyl-2-[(3'-N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Methyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate in 61% yield by the general procedure.

1-Methyl-6-methyl-2-[3'-(N-methylaminocarbonyloxy)phenyl]imidazo-[1,2-a]pyridinium Iodide. [DD-III-53; BM06699].

6-Methyl-2-(3'-N-methylaminocarbonyloxyphenylimidazo[1,2-a]pyridine (3.5 g, 12.4 mmol) was quaternized and recrystallized from acetonitrile/ethyl acetate to give 3.6 g (62%) of the desired product: mp 119-121°C; IR (KBr) 3500, 3200, 3000, 1720, 1520, 1230 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.7 (d, 3H); 3.95 (s, 3H); 7.35 (ds, 1H); 7.5 (m, 2H); 7.6 (t, 1H); 7.75 (q, 1H); 8.2 (d, 1H); 8.5 (s, 1H); 8.75 (s, 1H).

Anal Calcd. for $C_{17}H_{18}N_3O_2I$: C, 48.24; H, 4.28; N, 9.92; I, 29.98.
Found: C, 48.15; H, 4.29; N, 9.98; I, 30.06.

6-Chloro-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Chloro-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate in 61% yield by the general procedure.

1-Methyl-6-chloro-2-[4'-(N-methylaminocarbonyloxy)phenyl]imidazo-[1,2-a]pyrdinium iodide. [DD-III-55; BM06706].

The above 6-chloroimidazopyridine carbamate intermediate (3.5 g, 11.5 mmol) was quaternized and recrystallized with acetonitrile/ether to give 3.1 g (60%) of the desired product: mp 310-312°C; IR (KBr) ^{1}H NMR (DMSOd_6) δ 2.7 (d, 3H); 3.95 (s, 3H); 7.4 (d, 2H); 7.7 (d, 2H); 7.8 (q, 1H, D_2O exchangable) 8.15 (d, 1H); 8.35 (d, 1H); 8.5 (s, 1H); 9.25 (s, 1H). 3250, 3000, 1720, 1500, 1200 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}N_3O_2ClI$: C, 43.33; H, 3.40; N, 9.47; Cl, 7.99; I, 28.60.
Found: C, 43.43; H, 3.42; N, 9.51, Cl, 7.92; I, 28.69.

6-Chloro-2-[4'-(N,N-dimethylaminocarbamyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Chloro-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine was carbamoylated (Method A) to give the desired carbamate in 88% yield.

1-Methyl-6-chloro-2-[4'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium chloride. [DD-III-61;BM07641].

A solution of the above 6-chloro carbamate intermediate (5.0 g, 15.8 mmol) was quaternized and the iodide salt thus obtained was exchanged to a chloride salt. The product was obtained in 70% yield; mp 263°C; IR (KBr) 3440, 3100, 2950, 1700, 1600, cm^{-1}; ^{1}H NMR (DMSOd_6) δ 2.9 (s, 3H); 3.05 (s, 3H); 3.95 (s, 3H); 7.4 (d, 2H); 7.7 (d, 2H); 8.2 (dd, 1H); 8.4 (d, 1H); 8.6 (s, 1H); 9.35 (s, 1H).

Anal. calcd for $C_{17}H_{17}N_3O_2Cl_2 \cdot 0.5H_2O$: C, 54.71; H, 4.83; N, 11.19; Cl, 18.89.
Found: C, 54.47; H, 4.82; N, 11.21; Cl, 18.96.

6-Chloro-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Chloro-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate using Method A in 95% yield.

1-Methyl-6-chloro-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Chloride. [DD-III-100;BM07669].

A solution of the 6-chloro carbamate intermediate (4.0 g, 11.8 mmoles) was quaternized and converted to its chloride salt as described above. The desired product was obtained in 74% yield; mp. 260°C; IR (KBr) 3400, 3050, 2950, 1700, 1580 cm^{-1}; ^{1}H NMR (DMSOd_6) δ 2.9d (s, 3H); 3.05 (s, 3H); 3.95 (s, 3H); 7.4 (d, 1H); 7.5-7.56 (m, 2H); 7.65 (t, 1H); 8.2 (d, 1H); 8.4 (d, 1H); 8.5 (s, 1H); 9.2 (s, 1H).

Anal. calcd for $C_{17}H_{17}N_3O_2Cl_2$: C, 55.74; H, 4.68; N, 11.47; Cl, 19.36.
Found: C, 55.50; H, 4.64; N, 11.40; Cl, 19.47.

6-Chloro-2-[3'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Chloro-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate by the general procedure in 96% yield.

1-Methyl-6-chloro-2-[3'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Iodide. [DD-III-101; BM07678.

A suspension of the 6-chloro N-methylcarbamate intermediate was quaternized by the usual procedure to give the desired product in 78% yield; mp. 185-187°C; IR (KBr) 3300, 3100, 3040, 3000, 1720, 1580 cm^{-1}; ^1H NMR (DMSOd_6) δ 2.65 (d, 3H); 3.95 (s, 3H); 7.35 (d, 1H); 7.4-7.55 (m, 2H); 7.6 (t, 1H); 7.75 (q, 1H); 8.2 (dd, 1H); 8.35 (d, 1H); 8.5 (s, 1H); 9.25 (s, 1H).

Anal. calcd for $C_{16}H_{15}N_3O_2Cl$: C, 43.33; H, 3.40; N, 9.47; Cl, 7.99; I, 28.60.
Found: C, 43.25; H, 3.42; N, 9.40; Cl, 8.03; I, 28.67.

6-Trifluoromethyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Trifluoromethyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate (Method A) in 81% yield.

1-Methyl-6-trifluoromethyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]-midazo[1,2-a]pyridinium Chloride. [DD-III-112;BM07687.

A solution of 6-trifluoromethyl-2-[3'-(N,N-dimethylaminocarbonyloxy)-phenyl]imidazo[1,2-]pyridine was quaternized and converted to the chloride salt in 88% yield; mp 248-250°C, IR (KBr) 3300; 3080; 2980; 1710, 1660, 1530 cm^{-1}; ^1H NMR (DMSOd_6) δ 2.9 (s, 3H); 3.05 (s, 3H), 4.0 (s, 3H); 7.4 (d, 1H); 7.5-7.55 (m, 2H); 7.65 (t, 1H); 8.4 (d, 1H); 8.55 (d, 1H); 8.8 (s, 1H); 9.8 (s, 1H).

Anal. calcd for $C_{18}H_{17}N_3O_2F_3Cl$: C, 54.07; H, 4.28; N, 10.51; Cl, 14.25.
Found: C, 53.81; H, 4.33; N, 10.40; Cl, 8.75.

6-Trifluoromethyl-2-[3'-(N-methylaminocarbonyloxy)imidazo[1,2-a]pyridine.

6-Trifluoromethyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine was converted to the desired carbamate by the general procedure in 82% yield.

1-Methyl-6-trifluoromethyl-2-[3'-(N-methylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Iodide. [DD-III-117;BM7703.

A solution of 6-trifluoromethyl-2-[3'-N-methylaminocarbonyloxy)-phenyl]imidazo[1,2-a]pyridine (2.4 g, 7.4 mmol) was quaternized as described above to give the desired salt in 82% yield; mp 147-150°C; IR (KBr) 3200, 3000, 1730, 1660, 1575 cm^{-1}; ^1H NMR (DMSOd_6) δ 2.65 (d, 3H); 4.0 (s, 3H); 7.4 (d, 1H); 7.5-7.55 (m, 2H); 7.65 (t, 1H); 7.75 (q, 1H); 8.4 (d, 1H); 8.55 (d, 1H); 8.6 (s, 1H); 9.6 (s, 1H).

Anal. calcd for $C_{17}H_{15}N_3O_2F_3I$: C, 42.78; H, 3.168; N, 8.80; I, 26.59.
Found: C, 42.84; H, 3.18; N, 8.75; I, 26.67.

2-Chloro-3-methoxypyridine

A suspension of finely pulverized potassium hydroxide (8.6 g, 15.3 mmole) in dimethylsulfoxide (25 mL) was stirred for 5-10 min. To it was added 2-chloro-3-hydroxypyridine (5.0 g, 38.5 mmol) and the mixture was stirred at 55-60°C for 1h. A solution of iodomethane (4.8 mL, 10.945, 77 mmol) in dimethyl-sulfoxide (10 mL) was then added (at 55°C) over a period of 20 min. The reaction mixture was stirred for 2 h at the same temperature and then poured into ice water (200 mL). The solid obtained was then filtered and dried to give the desired 2-chloro-3-methoxypyridine (3.1 g, 56%). The aqueous filtrate was extracted with ethyl acetate (2x50 mL) and the organic layer was washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give an additional amount of product (1.2 g, 21%).

6-Nitro-2-chloro-3-methoxypyridine

A solution of 2-chloro-3-methoxypyridine (10.5 g, 73 mmole) in conc H_2SO_4 (15 mL) was added to a mixture of fuming nitric acid (50 mL) and conc H_2SO_4 (50 mL). The reaction mixture was heated to 90° and stirred at that temperature for 1 h. The mixture was then carefully poured onto crushed ice and neutralized with conc ammonium hydroxide. The precipitate obtained was then filtered and dried to give 9.45 g (68.5%) of the desired nitro derivative.

2-Amino-5-methoxypyridine<11>

A suspension of 2-chloro-3-methoxy-6-nitropyridine (6.0 g, 31.8 mmole) and 10% Pd/C (1.0 g) in ethanol (10 mL) was treated with a solution of sodium hypophosphite (8.8 g, 83.0 mmoles) in water (100 mL). The mixture was heated to reflux for 6-8 h, and filtered through Celite. The filtrate was cooled in ice, neutralized with saturated sodium bicarbonate solution and extracted with methylene chloride (3x25 mL). The organic layer was dried (Na_2SO_4) and evaporated <u>in vacuo</u> to give a red oil (3.64 g, 92%). The product was characterized by NMR and used without purification for the next reaction.

6-Methoxy-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 5-methoxy-2-aminopyridine and 4-hydroxy-α-bromoacetophenone were refluxed to give the desired 6-methoxy-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine in 74% yield.

6-Methoxy-2-[4-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine.

6-Methoxy-2-(4-hydroxyphenyl)imidazo[1,2-a]pyridine was carbamoylated (Method B) to give the desired carbamate in 77% yield.

1-Methyl-6-methoxy-2-[4'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Chloride. [DD-111-115;BM07696.

A solution of 6-methoxy-2-(4'-(N,N-dimethylaminocarbonyloxy)-phenyl)imidazo[1,2-a]pyridine (3.5 g, 11.2 mmoles) was quaternized and converted to its chloride salt in 75% yield; mp 215-216°C; IR (KBr) 3300, 3000, 1710, 1500, 1380 cm^{-1}; ^1H NMR ($DMSOd_6$) δ 2.9 (s, 3H); 3.05 (s, 3H); 3.87 (s, 3H); 3.92 (s, 3H); 7.35 (d, 2H); 7.7 (d, 2H); 7.85 (dd, 1H); 8.2 (d, 1H); 8.45 (s, 1H); 8.75 (s, 1H).

Anal. calcd for $C_{18}H_{20}N_3O_3Cl \cdot H_2O$: C, 56.91; H, 5.83; N, 11.06; Cl, 9.33.
Found: C, 56.88; H, 5.84; N, 11.04; Cl, 9.32.

6-Nitro-2-phenylimidazo[1,2-a]pyridine.

A suspension of 5-nitro-2-aminopyridine and phenacyl bromide were refluxed to give the desired imidazopyridine in 64% yield.

6-Amino-2-phenylimidazo[1,2-a]pyridine.

To a suspension of 6-nitro-2-phenylimidazo[1,2-a]pyridine (13.0 g, 57 mmol) and 10% Pd/C (0.700) in ethanol (130 mL) was added to a solution of sodium hypophosphite (26.0 g, 245 mmol) in water (130 mL). The reaction mixture was refluxed for 3 h and filtered through Celite. The Celite layer was then washed with water and the combined filtrate and washings were neutralized with saturated sodium bicarbonate solution. The precipitate thus obtained was filtered, dried to give the desired amine in 9.2 g (82%) yield.

6-(Methoxycarbonylamino)-2-phenylimidazo[1,2-a]pyridine.

A suspension of 6-amino-2-phenylimidazo[1,2-a]pyridine (3.5 g) and sodium carbonate (10.0 g, 94.3 mmol) in water/acetone (1:1, 100 mL) was cooled to 0°C

and methyl chloroformate (7.5 mL, 97.0 mmol) was added to it in a dropwise manner over a period of 10-20 min. After the addition was complete the mixture was allowed to warm to room temperature and stirred for 1.5h. The precipitate obtained was filtered, washed thoroughly with water and dried to give the desired carbamate in 3.6 g (80%) yield.

1-Methyl-2-phenyl-6-(methoxycarbonylamino)imidazo[1,2-a]pyridinium Chloride. [DD-III-62;BM07650.

A solution of 2-phenyl-6-methoxycarbonyloxyaminoimidazo[1,2-a]pyridine (3.5 g 13.0 mmol) was quaternized and converted to the chloride in 74% yield; mp 225-227°C; IR (KBr) 3180, 3170, 3040, 1720, 1590, 1540 cm^{-1}; ^1H NMR (D_2O) δ 3.75 (s, 3H); 3.9 (s, 3H); 7.6 (s, 5H); 7.75 (dd, 1H); 7.9 (d, 1H); 8.05 (s, 1H); 8.95 (s, 1H).

Anal. calcd for $C_{16}H_{16}N_3O_2Cl$: C, 60.47; H, 5.07; N, 13.22; Cl, 11.15.
Found: C, 60.32; H, 5.09; N, 13.11; Cl, 11.07.

6-Methoxy-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 5-methoxy-2-aminopyridine(3.9 g, 31.4 mmol) and 3-hydroxyphenacyl bromide (6.7 g, 31.16 mmol) in acetone (100 mL) was heated as described in the general procedure to give the desired product (5.6 g, 74%).

7-Methyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine.

A solution of 4-methyl-2-aminopyridine (5.0 g, 46.2 mmol) and 4-hydroxyphenacyl bromide (11.2 g, 52.0 mmol) in acetone (100 mL) was heated to reflux for 24 h and worked up as described in the general procedure, to give the desired product (8.5 g, 82%).

7-Methyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine.

Was prepared in 79% yield by the general procedure using 3-hydroxyphenacyl bromide as the starting material.

6-Hydroxy-2-phenylimidazo[1,2-a]pyridine.

A solution of 6-benzoyloxy-2-aminopyridine (5.8 g, 27 mmol) and phenacyl bromide (8.5 g, 42 mmol) in acetonitrile (100 mL) was refluxed as described in the general procedure. The precipitate obtained was warmed in 10% sodium hydroxide solution and the solution obtained was cooled and acidified with 10% hydrochloric acid. The precipitate obtained was filtered and dried to give the desired product (4.6 g, 82%).

2-Chloromethylimidazo[1,2-a]pyridine.

A solution of 1,3-dichloroacetone (11.0 g, 86.6 mmol) and 2-aminopyridine (8.4 g, 89.2 mmol) in acetone (200 mL) was heated to reflux for 24 h. The precipitate was dissolved in 10% hydrochloric acid and heated to reflux for 1 h. The solution was cooled in an ice bath and neutralized with sodium bicarbonate. The precipitate obtained was filtered and dried to give the desired product in 72% yield.

6-Methoxy-2-[3-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine was synthesized by General Method B to give 56% of the desired product.

7-Methyl-2-[4-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine was obtained in 69% yield by using General Method A.

7-Methyl-2-[3-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridine was obtained in 72% by using Method A.

6-(N,N-Dimethylaminocarbonyloxy)-2-phenylimidazo[1,2-a]pyridine: 6-Hydroxy-2-phenylimidazopyridine was converted to the desired carbamate by using Method A.

2-[3-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]imidazo[1,2-a]pyridine: A solution of 3-hydroxyphenylN,N-dimethylcarbamate (4.75 g, 26.0 mmol) and powdered potassium hydroxide (1.33 g, 23.7 mmol) in DMSO (15 mL) was stirred for 15-20 min. To this was added 2-chloromethylimidazo[1,2-a]pyridine (3.49 g, 20.9 mmol) in DMSO (15 mL). The reaction mixture was warmed to 55°C and stirred at that temperature of 1-1.5h. The mixture was then poured onto ice and extracted with ethyl acetate. The organic layer was washed with water two to three times, dried, and evaporated *in vacuo*, to give the desired product as an oil (5.53 g, 68%).

1-Methyl-7-methyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Chloride (DD-III-146; BM08611).

A solution of 7-methyl-2-(3'-hydroxyphenyl)imidazo[1,2-a]pyridine N,N-dimethyl carbamate was quaternized as usual. The desired product was obtained in 70% yield, mp 236-238°C; IR (KBr) 3500, 3000, 1740, 1710, 1650, 1540 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.6 (s, 3H); 2.9 (s, 3H); 3.05 (s, 3H); 3.9 (s, 3H); 7.35-7.65 (m, 5H); 8.1 (s, 1H); 8.55 (s, 1H); 8.85 (d, 1H).

Anal. calcd for $C_{18}H_{20}N_3O_2Cl$, 1.5 H_2O: C, 58.08; H, 6.22; N, 11.28; Cl, 9.52;
Found: C, 58.25; H, 6.22; N, 11.25, Cl, 09.52.

1-Methyl-7-methyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Chloride (DD-III-147; BM08620).

A solution of 7-methyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridine N,N-dimethyl carbamate was quaternized as usual. The product was obtained in 73% yield; mp 228-230°C; IR (KBr) 3400, 3010, 1730, 1660, 1530, 1500; ^{1}H-NMR (DMSOd_6) δ 2.55 (s, 3H); 2.85 (s, 3H); 3.0 (s, 3H); 3.85 (s, 3H); 7.3-7.45 (m, 3H); 7.7 (d, 2H); 8.1 (s, 1H); 8.5 (s, 1H); 8.8 (d, 1H).

Anal. calcd for $C_{18}H_{20}N_3O_2Cl \cdot 0.5H_2O$: C, 60.92; H, 5.96; N, 11.84; Cl, 9.99;
Found: C, 60.82; H, 5.99; N, 11.78; Cl, 10.06.

1-Methyl-6-methoxy-2-[3'-(N,N-dimethylaminocarbonyloxy)phenyl]imidazo[1,2-a]pyridinium Cloride (DD-III-158; BM08639). A solution of 6-methoxy-2-(3'-hydroxyphenyl)imidazo-[1,2-a]pyridine N,N-dimethyl carbamate was quaternized as usual. The product was obtained in 61% yield; mp 220-223°C; IR (KBr) 3400, 3000, 1740, 1540-, 1500 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.9 (s, 3H); 3.05 (s, 3H); 3.9 (d, 6H); 7.35 (d, 1H); 7.5 (m, 2H); 7.6 (t, 1H); 7.85 (d, 1H); 8.2 (d, 1H); 8.5 (s, 1H); 8.75 (s, 1H).

Anal. calcd for $C_{18}H_{20}N_3O_3Cl \cdot 0.25H_2O$: C, 59.01; H, 5.57; N, 11.47; Cl, 9.67;
Found: C, 58.83; H, 5.68; N, 11.36, Cl, 9.65.

1-Methyl-6-[N,N-dimethylaminocarbonyloxy]-2-phenylimidazo[1,2-a]pyridinium Chloride (DD-III-174; BM08648).

A solution of 6-hydroxyl-2-phenylimidazo[1,2-a]pyridine N,N-dimethyl carbamate was quaternized as described in the general aprocedure and the product was recrystallized from t-butanol/ether. The product was obtained in 54% yield; mp 128-130°C; IR (KBr) 3400, 3000, 1680, 1540, 1480, 1450 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.9 (s, 3H); 3.05 (s, 3H); 3.95 (s, 3H); 7.6-7.7 (m, 5H); 8.0 (d of d, 1H); 8.35 (d, 1H); 8.65 (s, 1H); 9.35 (s, 1H).

Anal. calcd for $C_{17}H_{18}N_3O_2Cl \cdot 1H_2O$: C, 58.36; H, 5.76; N, 12.00; Cl, 10.13;
Found: C, 58.45; H, 5,77; N, 12,00; Cl, 10.18.

1-Methyl-2-[3'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl]imidazo[1,2-a]pyridinium Chloride (DD-III-178; BM08657).

A solution of the appropriate carbamate was quaternized as described above except that the product was recrystallized from isopropanol/ether. The desired product was obtained in 71% yield; mp 220°C; IR (KBr) 3400, 1720, 1650, 1600, 1540 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.9 (s, 3H); 3.0 (s, 3H); 4.0 (s, 3H); 5.5 (s, 2H); 6.75 (d, 1H); 6.9 (s, 1H); 6.95 1(d, 1H); 7.3 (t, 1H); 7.55 (t, 1H); ;8.0 (t, 1H); 8.25 (d, 1H); 8.55 (s, 1H); 8.95 (d, 1H).

Anal. calcd for $C_{18}H_{20}N_3O_3Cl \cdot 1.25H_2O$: C, 56.24; H, 6.03; N, 10.93; Cl, 9.22;
Found: C, 55.99; H, 5.93; N, 10.84; Cl, 9.29.

General Procedure for Preparation of Quaternary Heteroaromatic Phenoxymethyl Carbamates.

The appropriate hydroxyphenyl carbamate (1.2 equiv) was dissolved in DMSO and added to a suspension of potassium hydroxide (1.4 equiv) in DMSO in a dropwise manner. The mixture was stirred for 30 min. To this reaction mixture was added potassium carbonate (1.0 equiv) followed by a dropwise addition of a solution of the heteroaryl methyl chloride hydrochloride salt (1.0 equiv) in DMSO. The reaction mixture was stirred overnight at room temperature and poured into ice water. If a precipitate was obtained, it was filtered. Products which were oils were extracted with ethyl acetate and the organic layer washed with water, dried and evaporated to give the desired heteroaryl phenoxymethyl carbamate.

1,3-Dimethyl-2-[4'(N,N-dimethylaminocarbonyloxy)phenoxymethyl]benzimidazolium Chloride (DD-III-194A; BM09305)

The title compound was prepared by the general procedure in 42% yield: mp 210-212°C; IR (KBr) 3400, 3020, 1730, 1400, 1340 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.85 (s, 3H); 3.0 (s, 3H); 4.1 (s, 6H); 5.8 (s, 2H); 7.1 (q, 4H); 7.7 (q, 2H); 8.05 (q, 2H).

Anal. calcd for $C_{19}H_{22}N_3O_3Cl \cdot 1.25\ H_2O$: C, 57.28; H, 6.07; N, 10.54; Cl, 8.89
Found: C, 57.36; H, 6.11; N, 11.18; Cl, 9.43

1,3-Dimethyl-2-[3'(N,N-dimethylaminocarbonyloxy)phenoxymethyl]benzimidazolium Chloride (DD-III-193; BM09298)

The title compound was prepared by the general procedure in 41% yield: mp 139-141°C; IR (KBr) 3400, 1750, 1620, 1550, 1490 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.85 (s, 3H); 3.0 (s, 3H); 4.15 (s, 6H); 5.8 (s, 2H); 6.8 (d, 1H); 7.0 (m, 2H); 7.35 (t, 1H), 7.7 (q, 2H); 8.05 (q, 2H).

Anal. calcd for $C_{19}H_{22}N_3O_3Cl \cdot 1.0\ H_2O$: C, 57.93; H, 6.14; N, 10.66; Cl, 9.00
Found: C, 57.92; H, 6.17; N, 10.63; Cl, 8.97

1-Methyl-2-[4'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl)quinolinium chloride. (DD-IV-15; BM09323)

The title compound was prepared as described in the 43% yield: mp 188-190°; KBr) 3450, 3400, 1720, 1630, 1620, 1600 cm^{-1}; ^{1}H-NMR (D_2O) δ 2.95 (s, 3H); 3.1 (s, 3H); 4.55 (s, 3H); 5.8 (s, 2H); 7.05-7.2 (q, 4H); 8.0 (t, 1H); 8.2-8.35 (m, 3H); 8.5 (d, 1H); 9.1 (s, 1H).

Anal. calcd for $C_{20}H_{20}N_2O_3Cl \cdot 1.5H_2O$: C, 60.22; H, 5.81; N, 7.02; Cl, 8.88;
Found: C, 60.06; H, 6.00; N, 7.06; Cl, 9.00

1-Methyl-2-[3-(N,N,-dimethylaminocarbonyloxy)phenoxymethyl]quinolinium Chloride. (DD-IV-10; BM0934)

The chloride salt was prepared according to the general procedure described

above in 58 % yield: mp 197-199°C; IR (KBr) 3400, 3030, 1730, 1610, 1530 cm^{-1} 1 H-NMR (D_2O) δ 2.9 (s, 3H); 3.10 (s, 1H); 4.5 (s, 3H); 5.75 (s, 2H); 6.8 (d, 1H); 6.9 (s, 1H); 7.05 (d, 1H); 7.35 (t, 1H); 8.0 (t, 1H); 8.2-8.35 (m, 3H); 8.5 (d, 1H); 9.05 (d, 1H).

Anal. calcd. for $C_{20}H_{20}N_2O_3Cl \cdot 1.25H_2O$: C, 60.91; H, 5.75; N, 7.10; Cl, 8.98
Found: C, 60-70; H, 5.93; N, 7.05; Cl, 9.02

1-Methyl-2-[2'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl]pyridinium Bromide. (DD-IV-16; BM09332)

The compound was prepared according to the general procedure, and the iodide salt obtained was passed through a bromide ion exchange column. The product was obtained in 47% yield: mp 186-188°C; IR (KBr) 3460; 3000, 1745, 1640, 1510 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.9 (s, 3H); 3.1 (s, 3H); 4.3 (s, 3H); 5.65 (s, 2H); 7.05 (t, 1H); 7.2 (m, 2H); 7.35 (d, 1H); 7.95-8.1 (m, 2H); 8.65 (t, 1H); 9.1 (d, 1H).

Anal. calcd. for $C_{16}H_{19}N_2O_3Br \cdot 0.75\ H_2O$: C, 50.47; H, 5.38; N, 7.35; Br, 20.98
Found: C, 50.69; H, 5.34; N, 7.36; Br. 20.84

1,3-Dimethyl-2-[2'-(N,N-dimethylaminocarbonyloxy)phenoxymethyl]imidazolium Iodide (DD-IV-20; BM09341)

The compound was prepared by the procedure described above. The yield of the product was 69%; mp 144-145°; IR (KBr) 3500, 3110, 1720, 1600, 1550 cm^{-1}; ^{1}H-NMR (DMSOd_6) δ 2.8 (s, 3H); 2.9 (s, 3H); 3.8 (b, 6H); 5.5 (s, 2H); 7.0-7.1 (m, 2H); 7.2-7.35 (m, 2H); 7.75 (s, 2H).

Anal. calcd. for $C_{15}H_{20}N_3O_3I$: C, 43.17; H, 4.83; N, 10.07; I, 30.41
Found: C, 43.25; H, 4.86; N, 10.10; I, 30.35

4-(N,N-Dimethylaminocarbonyloxy)phenoxyacetonitrile

A suspension of potassium carbonate (7.74 g, 0.56 mol) in DMSO (100 mL) was treated with a solution of 4-hydroxyphenyl carbamate (7.64 g, 0.042 mol) in DMSO (100 mL). The mixture was stirred for 1½ h at room temperature and then treated with a solution of chloroacetonitrile (3.94 mL, 0.626 mol) in DMSO (10 mL) in a dropwise manner. The reaction mixture was allowed to stir at room temperature for 3-4 h and then poured over ice water. The precipitate obtained was filtered, washed with water and dried in air to give the desired product (6.9 g, 75.1%). The product was characterized by NMR and used for the next step.

3-(N,N-Dimethylaminocarbonyloxy)phenoxyacetonitrile

The compound was prepared from chloroacetonitrile and 3-hydroxyphenyl N,N-dimethylcarbamate by the general procedure to get the product in 79% yield. The product was characterized by NMR and used for the next step without further purification.

2-[4'-(N,N-Dimethylaminocarbonyloxy)phenoxymethyl]benzimidazole

The method of Nabulski and Gandour was followed.<12>
To a solution of 4-(N,N-dimethylaminocarbonyloxy)phenoxyacetonitrile (5.0 g, 0.022 mol) in methanol (80 mL) was added sodium (0.52 g, .022 gatom). The solution was allowed to stir at room temperature for 2 h. The reaction mixture was then quenched with ice water and the turbid solution was extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated <u>in vacuo</u> to give an oil (5.6 g, 70%). The product was characterized by NMR and used for the next step without further purification.

2-[3'-(N,N-Dimethylaminocarboyloxy)phenoxymethyl]benzimidazole

The compound was prepared by the same procedure as for the 4-isomer. The desired product was obtained in 68% yield. The product was characterized by NMR and used for the next step without further purification.

Procedure for Determination of Acetylcholinesterase Inhibition

In a typical run a predetermined amount of test compound (0, 10, 30 and 100 uL) is placed in a photometric cuvette with 100 uL DNTB (5,5'-dithio-bis(2-nitrobenzoic acid), and 50 uL of enzyme (acetylcholinesterase, eel type III). A final volume of 3 mL is obtained by adding the corresponding amount of buffer (52 mM NaH_2PO_4) to the mixture. This mixture is incubated at room temperature for 10 to 15 minutes. The mixture at that point constitutes blank or background.

The apparatus used to follow the reaction is a Hewlett Packard 8452A diode array spectrophotometer. After the incubation period is completed, 100 uL of acetylthiocholine iodide is added and allowed to stir for about 30 seconds and immediately placed in the spectrometer. At this time the absorption of the solution is measured and collected at 412 nm every thirty seconds for 6 min. From the slope of the curve obtained the rate of the enzymatic reaction, the hydrolysis of substrate, is determined.

The IC_{50} or inhibitor coefficient at which half of the enzyme is inhibited is obtained from the plot of the percentage enzymatic activity (%EA) versus the logarithm of the inhibitor concentration. The %EA is determined by dividing the slope (or rate) from the corresponding inhibitor by the average slope (or rate) of the control.

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